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VIVAX RELAPSE RATES FOLLOWING CONTINUED ATABRINE SUPPRESSIVE MEDICATION: OBSERVATIONS ON MALARIA IN AN INFANTRY REGIMENT*†

BENJAMIN M. BAKER,[1] AND DAVID PLATT,[2,3]

Received for publication July 7, 1947

I. INTRODUCTION

A. The 147th Infantry Regiment served on various islands of the Pacific from the first half of 1942 to September, 1945. The malaria experience of the regiment, consisting of exposures to malaria of varying severity, atabrinization and deatabrinization, carefully recorded by different observers (1) (2), provides a basis for the study of several important problems concerning the control of the relapsing characteristic of vivax malaria. A period of heavy exposure was followed first by six months withdrawal of suppressive medication, then by eighteen months of well-controlled suppressive atabrinization, with little or no fresh exposure, and finally by terminal deatabrinization.

Although the data are neither complete nor perfect from a scientific standpoint, nevertheless opportunities for comparable studies are

* Presented in slightly altered form before the meeting of the American Clinical and Climatological Association at Hershey, Pennsylvania, in October, 1946.

† Released for publication by the War Department, Office of the Surgeon General.

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[2] Former Captain, M.C., AUS, and Surgeon, 147th Infantry Regiment.

[3] This study depended upon a carefully planned series of sequential observations and the participation both directly and indirectly of many individuals too numerous to mention by name. The initial demalarialization plan was formulated by the joint Army and Navy South Pacific Malaria and Epidemic Control Organization, first under the leadership of Commander James J. Sapero, M.C., USN, later Commander Fred F. Butler, M.C. USN, and Lt. Col. Paul A. Harper, M.C., AUS, the representative of the United States Army Forces. Lt. Commander W. G. Reddick, M.C., USNR, managed the demalarialization in Samoa, and Lt. Col. Wilbur G. Downs, M.C. AUS, made a special analysis of the Samoa results. The regimental surgeons provided the continuity upon which depended an indispensable record of individual malaria attacks.

likely to be infrequent in the future. Therefore, the information provided by this study on the practical management of relapsing malaria in heavily seeded troops merits record and publication.

B. *Facts relevant to the subject.* 1. Atabrine (0.1 gms./day) will suppress the vast majority, if not all, primary or recurrent attacks of vivax malaria (3), but thus far has not been shown to cure the disease in the same way that most, if not all, cases of falciparum malaria are cured by a like regime (4).

2. An outstanding and *specific* characteristic of vivax malaria is its tendency to relapse (5). The frequency and intensity of relapse vary with the *strain* of *P. vivax* (6) and, undoubtedly, also with factors peculiar to the host (7).

3. The tendency of vivax malaria to relapse does not continue indefinitely, but ceases spontaneously after two, three or possibly more years in all strains upon which there is reliable information (8).

C. *Significant gaps in knowledge relevant to the subject.* 1. From the facts cited in paragraph B, it seems probable that the majority of the normal relapses from vivax malaria would be prevented over a period of two or three years provided suppressive atabrine were given continuously. For obvious reasons, this theoretic possibility has never been checked under satisfactorily controlled experimental conditions; therefore, the proposition has never been proved.

2. Assuming the proposition to be true, the academic, but nonetheless scientifically important, questions arise as to whether the latent vivax infections were merely suppressed temporarily or were extinguished as a result of a) the medication or b) the sheer passage of time and the development of biologic defense.

II. MATERIALS AND METHODS OF OBSERVATIONS

A. *Composition.* The regiment, a National Guard organization, was recruited largely from Ohio and contained no negroes. Training took place in the southern and southeastern parts of the United States in areas where on the whole malaria control was excellent. Although no information upon the amount of malaria acquired during training is available, it is altogether likely that it was negligible in amount and suppressive medication was not used until the regiment arrived in Guadalcanal.

B. *Pacific history.* The 147th Infantry Regiment arrived overseas

in two echelons, the first in April 1942 at Tonga, and the second in June 1942 at Fiji, neither of which islands is malarious. The First Battalion arrived at Guadalcanal, at the time a very malarious island, on 4 November 1942. Quinine sulphate, 0.3 gms. daily, was used as a malaria suppressive. The Third Battalion, plus special units, arrived 29 November 1942 and from that date atabrine, 0.4 gms. weekly, was the standard suppressive drug for all the regimental troops. The Second Battalion did not reach Guadalcanal until 7

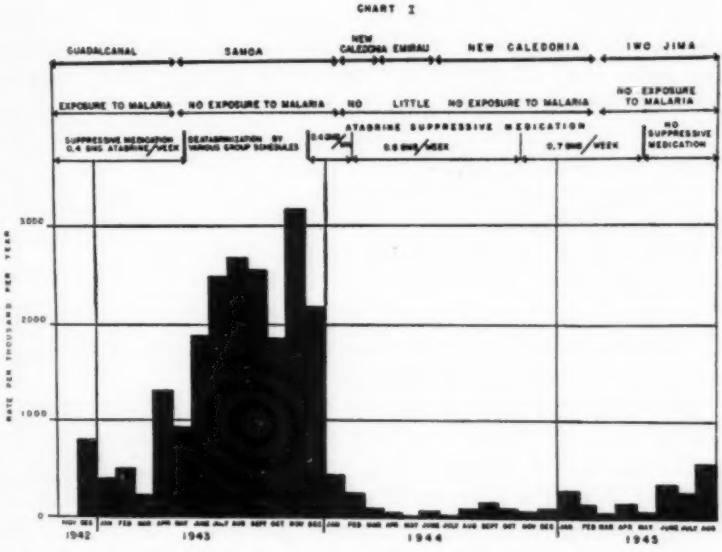

CHART I. MALARIA RATES, MALARIA EXPOSURE; ATABRINIZATION AND DEATABRINIZATION OF AN INFANTRY REGIMENT

February 1943. A few replacements previously unexposed to malaria joined the regiment during the middle of April. On 12 May 1943 the entire regiment left for British Samoa, a non-malarious island.

Thus the regimental components were exposed to hyperendemic malaria for periods varying from one to six months. During this exposure atabrine discipline was poor and even the introduction on 29 March 1943 of the roster system of administering the drug did nothing to lessen a high malaria rate (Chart I).

On Samoa, troops were released from atabrine suppressive medication. This project and its results are discussed in other reports and will be published in detail elsewhere by t heseveral observers concerned, but may be briefly summarized as follows. One group stopped atabrine suddenly. A second took atabrine 0.1 gm. t.i.d. for seven days, rested for ten days, took similar doses of atabrine for the next seven days, and then discontinued medication. A third group stopped atabrine completely for ten days and was then treated according to the schedule for the second group. The fourth group took atabrine 0.1 gm. t.i.d. for seven days, rested for two days, took plasmochin 0.01 gm. b.i.d. for five days, rested for ten days, then repeated the entire cycle of atabrine and plasmochin therapy before stopping all medication. The fifth group continued the suppressive atabrine schedule (0.4 gms. weekly) for six weeks and then discontinued the drug. All clinical attacks were treated as follows:

1. Quinine sulfate or hydrochloride 0.6 gm. t.i.d. with atabrine 0.1 t.i.d. for three days.
2. Atabrine 0.1 gm. t.i.d. for an additional four days.
3. Rest two days.
4. Plasmochin 0.01 gms. b.i.d. for five days. Patients were given no further antimalarial drugs unless other clinical attacks developed, which were then treated in the same manner.

Over ninety per cent of the men with long Guadalcanal exposure had at least one attack of malaria on Samoa; about eighty-five per cent relapsed at least once. The highest malaria rate developed in the first group the third week after stopping suppression, and exceeded fourteen thousand per thousand per year. The peak of the first observed relapses was reached the sixth week following the first clinical attacks. This sustained high level of clinical reactivation makes it clearly evident that the men in the 147th Infantry Regiment had been infected with strains of *P. vivax* of a highly relapsing character.

Since its working efficiency was so severely depleted, the entire regiment returned to supervised atabrine suppressive medication, 0.4 gm. per week on 26 November 1943. The malarial rate promptly declined on this dosage and late in January 1944 the amount of drug was increased to 0.6 gm. per week.

The regiment left Samoa on 3 February 1944 for New Caledonia, a nonmalarious area, and exactly two months later departed for the Island of Emirau. This island had a history of moderate incidence of malaria but it is not believed that high levels of transmission prevailed during the period—less than three months—that the 147th remained there (Table II). An extensive program of drainage and larviciding virtually eliminated anopheles breeding. Natives were removed to another island or were confined in a well-controlled area. Such transmission as may have occurred must have been due to the residual population of anopheline adults present when the troops arrived. Atabrine discipline was excellent.

Early in July the regiment left Emirau and returned to non-malarious New Caledonia, remaining for eight months, after which it departed for Iwo Jima, arriving there on 20 March 1945. This island is also free from malaria. Throughout all these movements the regimental troops continued to take suppressive atabrine, the only variation in the program being an increase commencing in November 1944 in the weekly dosage from 0.6 to 0.7 gms. per week. Once established on Iwo Jima, consideration was given once more to the desirability of deatabrinizing the remaining troops, and on 20 May 1945 the suppressive drug program was officially discontinued.

In summary, therefore, the 147th Infantry Regiment, following its malaria exposure on Guadalcanal and its various deatabrinization experiences on Samoa, took suppressive atabrine from 26 November 1943 (Samoa) to 20 May 1945 (Iwo Jima), a period of eighteen months.

III. OBSERVATIONS

This paper is concerned primarily with the relapse experience, with vivax malaria,[4] of the 147th Infantry Regiment after stopping atabrine suppressive medication. Observations were restricted to men who had remained with the organization from the beginning of their various group exposures on Guadalcanal until June, July or August, 1945. By September 1945 a considerable number of men had already been returned the United States and those remaining were being returned so rapidly that the observations were discontinued.

Not all of these men had equal periods of malaria exposure on

[4] All diagnoses were confirmed by the demonstration of parasites in blood films.

TABLE I

Monthly malaria attack rates per thousand per year by groups, November '42 through August '45

	GROUP A		GROUP B		GROUP C		TOTAL	
	six months*		three months*		one month*			
	Strength†	Rate	Strength†	Rate	Strength†	Rate	Strength	Rates
Nov. 42	89	0					0	0
Dec. 42	89	809					89	809
Jan. 43	89	405					89	405
Feb. 43	89	1215	332	325			421	513
Mar. 43	89	809	332	72			421	228
Apr. 43	89	1484	332	1300	23	522	444	1296
May. 43	89	1348	332	794	23	1043	444	918
Jun. 43	89	2022	332	1913	23	522	444	1863
Jul. 43	89	4315	332	1986	23	2609	444	2484
Aug. 43	89	5527	332	1986	23	1565	444	2673
Sep. 43	89	4448	332	2222	23	2609	444	2538
Oct. 43	89	3774	332	1336	23	1565	444	1836
Nov. 43	89	4315	332	2491	23	2609	444	3132
Dec. 43	89	405	332	2744	23	522	444	2160
Jan. 44	89	270	332	505	23	0	444	432
Feb. 44	89	270	332	253	23	0	444	243
Mar. 44	89	135	332	108	23	0	444	108
Apr. 44	89	0	332	72	23	0	444	54
May 44	89	0	332	0	23	522	444	27
Jun. 44	89	135	332	72	23	0	444	81
Jul. 44	89	135	332	0	23	0	444	27
Aug. 44	89	0	332	144	23	0	444	108
Sep. 44	89	405	332	108	23	0	444	162
Oct. 44	89	270	332	72	23	0	444	108
Nov. 44	89	135	332	72	23	0	444	81
Dec. 44	89	135	332	108	23	0	444	108
Jan. 45	89	270	332	217	23	1043	444	270
Feb. 45	89	135	332	108	23	522	444	135
Mar. 45	89	270	332	0	23	0	444	54
Apr. 45	89	270	332	108	23	0	444	135
May 45	89	0	332	108	23	0	444	81
Jun. 45	85	706	324	222	23	522	432	333
Jul. 45	81	444	273	220	23	0	377	255
Aug. 45	50	1200	218	330	15	800	283	509

* Time spent on Guadalcanal.

† Number of men remaining with regiment since arriving on Guadalcanal.

Guadalcanal. The differences are shown in Table I by groups, together with the respective relapse experiences of the groups.

It has been pointed out that the malaria exposure of the regiment on Emirau was not great. Table II gives the malaria rate of men who joined the regiment after it left Guadalcanal and provides strong evidence that malarialization of the regiment on Emirau was of little importance.

In brief, it is evident from the chart and the tables that the cessation of atabrine on 20 May 1945 was unattended by anything like the

TABLE II

Monthly malaria attack rates per thousand per year of 147th infantry men with Emirau but not Guadalcanal malaria exposure

Group D

	STRENGTH	RATE
Apr. 44	803	0
May 44	803	15
Jun. 44	803	45
Jul. 44	803	0
Aug. 44	803	45
Sep. 44	803	0
Oct. 44	803	0
Nov. 44	803	30
Dec. 44	803	0
Jan. 45	803	15
Feb. 45	803	15
Mar. 45	803	15
Apr. 45	803	15
May 45	803	0
Jun. 45	789	15
Jul. 45	767	16
Aug. 45	745	16

increase in attack rates observed following trial deatabrinization in Samoa almost exactly two years before. Very slight rate excesses in June, July and August over those of previous months are apparent but their significance is not known. It is unfortunate that observations could not have been continued longer to determine this point.

IV. DISCUSSION

As indicated above, vivax malaria relapses over a period of many months, the great bulk of clinical reactivity occurring within a year after the initial attack but extending over into the second and occasionally even the third years. This information is derived from

observations on both mosquito-induced therapeutic malaria and cases of naturally acquired malaria removed from the possibility of reinfection (5) (7) (9) (10). The actual frequency of reactivations after initial episodes is well known for the strain or strains of vivax malaria under discussion (2) (11), but it is well established, too, that different strains of vivax vary in respect to their characteristic relapse behavior (6).

It seems logical to infer on the basis of available information that a high degree of clinical activity would have manifested itself for at least a year, in some cases even longer, following the last attacks acquired on Guadalcanal, i.e., until June or July 1944. This inference is supported by the relapse experience of the 147th Infantry Regiment from June to November 1943, and also by the study of several groups of men who acquired malaria on Guadalcanal and when subsequently removed to non-malarious areas continued to exhibit reactivation for well over a year. Therefore, it is highly probable that the reduction in the number of relapses in this regiment after December 1943 was due to the resumption of suppressive atabrine and not to a spontaneous termination of clinical activity. This conclusion is justified even though we can not demonstrate what the curve of attack rates from January 1943 to May 1945 would have been in the absence of drug suppression. This curve could have been determined only by denying atabrine to a representative segment of the regiment, an experiment which under the circumstances was not feasible. Such a procedure, could it have been carried out, would have made a controlled experiment out of what must remain an uncontrolled, though informative, series of observations.

The continuation of suppressive atabrine medication in troops as heavily seeded as this regiment was a military necessity, for without it high malaria rates and serious disability would have prevailed. When necessity demanded that this plan be followed, serious consideration was given to the ultimate fate of such troops, but there were no data upon which to base reliable predictions. It was realized and feared that prolonged atabrine suppression might merely postpone the evil day, as was known to be the case when short term suppressive treatment was employed. Provided that a three months' period of

observation following final deatabrinization of heavily seeded troops is sufficient, the observations recorded here answer a very important question.[5] Not only is the high malaria rate of heavily seeded troops temporarily controlled by atabrine suppressive medication but a highly significant amount of clinical vivax malaria is permanently abolished.

V. CONCLUSIONS

1. It has been shown that standard suppressive atabrine treatment may be discontinued safely two years after the last exposure of heavily seeded troops without leading, within a period of three months, to an excessive reactivation rate.

2. Previous observations of the same troops proved that it was not safe to *stop* atabrine for at least six months after exposure.

3. It is generally accepted that four weeks of suppressive atabrine medication following the acquisition of P. falciparum infection prevents all further clinical activity. It appears from these observations that suppressive atabrine medication for eighteen months after significant exposure exerts a comparable effect upon *some* but *not all* cases of P. vivax infection.

4. This illustrates and confirms the general belief that heavily seeded troops should be taken off suppressive medication very cautiously. If the relapse characteristics of the strains involved resemble those of Guadalcanal strains, troops should not be taken off for at least six months. From then on suppressive medication should be withdrawn only from sample fractions to obtain some indication of the remaining relapse latencies. After two years it is probably safe to discontinue the suppressive drug program for all troops at the same time.

5. These observations are believed to indicate that, had it been possible to make troops ingest atabrine in suppressive doses faithfully and for a sufficiently long time after malaria exposure, clinical malaria in the armed forces might have been in large measure prevented.

[5] All men who participated in this study were requested to report their subsequent attacks of malaria to the senior author by letter. Up to January, 1947, only five attacks were reported.

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THE INFLUENCE OF HYPERVITAMINOSIS A ON BONE GROWTH

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Received for publication July 16, 1947

The objective of this experiment was to determine the effect of hypervitaminosis A on the longitudinal growth of the long bone of the rat. Collazo showed that large amounts of vitamin A will produce fractures in the long bones of growing rats (1) (2) (3). This work has been duplicated by others. The literature on the subject has been adequately reviewed by Wolbach and Bessey (4) and by T. Moore and Wong (5). Wolbach (6) has recently shown that the effect of hypervitaminosis A on the growing bone is a composite of several factors: first, a speeding up of maturation, degeneration and death of cartilage cells in the epiphysis; second, correspondingly active replacement bone formation with early closure of epiphyses that normally close, and third, concurrent acceleration of remodelling of the shaft of the bone, normal in location and execution, but sufficiently abnormal in rate so that the rapid replacement of strong old bone with new weak bone produces a structure insufficiently strong, because of the normal lag in calcification, to resist fracture under the strains imposed by normal activity. Remodelling of the long bone has been interpreted as a function of stress and strain for two reasons—first, bone adapts itself in external form and internal trabeculation so that a maximum of strength is achieved with a high degree of economy of material; second, as Glucksman (8) (9) has well shown, bone in tissue culture grows in such a form that it most efficiently resists the strains applied to it. It therefore seemed desirable to Wolbach to correlate the accelerated remodelling of bone resulting from excessive vitamin A administration with the rate of longitudinal growth of bone, in order to ascertain whether remodelling is solely the result of mechanical factors. This experiment was therefore performed in his laboratory, under his direction, to ascertain whether or not an increased rate of longitudinal growth was present.

[1] Present address Johns Hopkins Hospital, Baltimore, Maryland.

MATERIALS AND METHODS

The experiment consisted essentially of measuring longitudinal growth of the left tibia, body weight, and food intake of a number of rats given varying excessive doses of vitamin A.

The rats were albino rats of the Wistar strain, obtained from the Harvard Biological Laboratories. They were 21 day old "weanlings" at the onset of the experiment.

The vitamin A used was winterized, vitamin A concentrate, containing 500,000 international units per gram, distilled from fish liver and vegetable oils by Distillation Products, Inc. This compound contains vitamin A 14.3%, unidentified sterols less than 10%, tocopherols less than 1% in solution in distilled fat. The vitamin D content is well under 100 units per gram. (10) This preparation was administered orally, the given amount being placed on the back of the animal's tongue. The dosage of vitamin A, the number of animals treated, and the duration of the experiment is indicated in the graph summarizing the results. It was previously determined (4) (6) that crystalline vitamin A (obtained from the Distillation Products, Inc., Rochester, New York) produced all of the bone changes concerned in this experiment.

Bone growth was measured by taking weekly roentgenograms of the left tibia. To eliminate the necessity of using anesthesia, a special frame was designed for holding the animals motionless (Fig. 1). It was not difficult to secure the animals by tightening the tapes with the peg-winches and proper application of the spring clips. The distance on the roentgenograms between the midpoints of the proximal and distal ends of the bone was measured with calipers and considered to represent the length of the bone. With the x-ray tube set at a target-film distance of 90 cm. to insure perpendicular rays, minor variations in the position of the leg inherent in this technique did not introduce an error of more than 0.1 mm. Measurements with considerable comparative value, therefore, could be obtained.

Weight gain was followed by weighing the animals daily. Food intake was measured each day. Purina dog chow checkers were used as food. An amount somewhat above the daily expected intake was weighed out and put into the cages. At the end of twenty-four hours,

the intake was calculated after weighing the residue. The animals were housed in separate cages with wire mesh floors which allowed a certain loss of food, introducing an error into these measurements; however, being relatively constant throughout, this loss did not

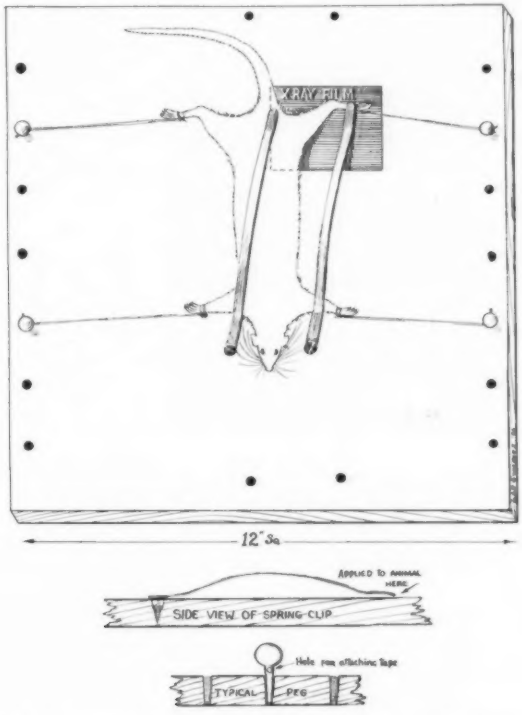

FIG. 1. APPARATUS FOR HOLDING ANIMALS WHILE ROENTGEONGRAMS ARE BEING TAKEN

particularly distort the comparative value of the figures obtained. The animals were allowed free access to water.

Alterations in the gross morphology of the left tibia were followed by roentgenograms and observation of the bone at autopsy. Changes in histology were followed by study of microscopic sections.

RESULTS

Weanling rats receiving 250, 275, 625, or 1250 international units of vitamin A per gram of body weight per day developed changes in the left tibia similar to those described by Wolbach (6).

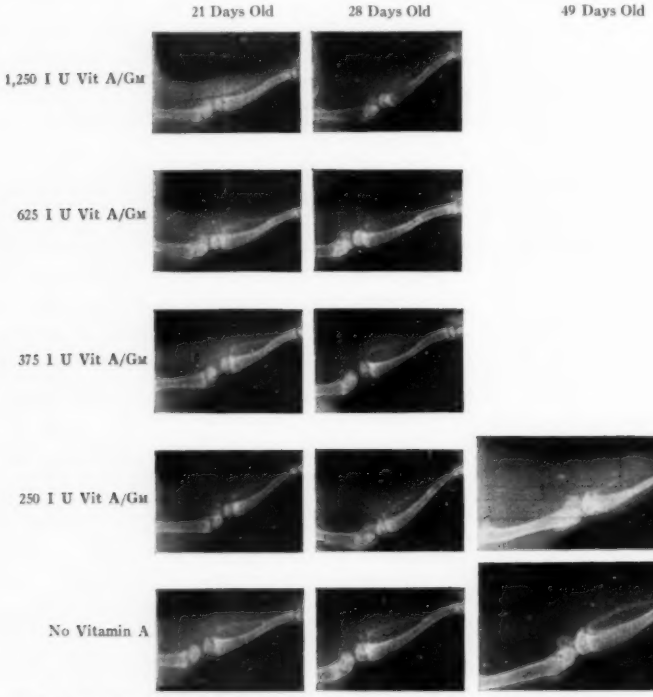

FIG. 2. The influence of hypervitaminosis A on the gross morphology of the left tibia of the growing rat as revealed by roentgenograms. The indicated amount of vitamin A was given every day beginning just after the "21 days old" X-ray was taken.

The gross changes are shown in the reproductions of the roentgenograms in Figure 2. The bones are seen to be more slender than normal controls. The cortex of the metaphysis is less opaque to the roentgen ray. The epiphyseal cartilage is decreased in width. Within the range of dosage used, the greater the amount of vitamin A given,

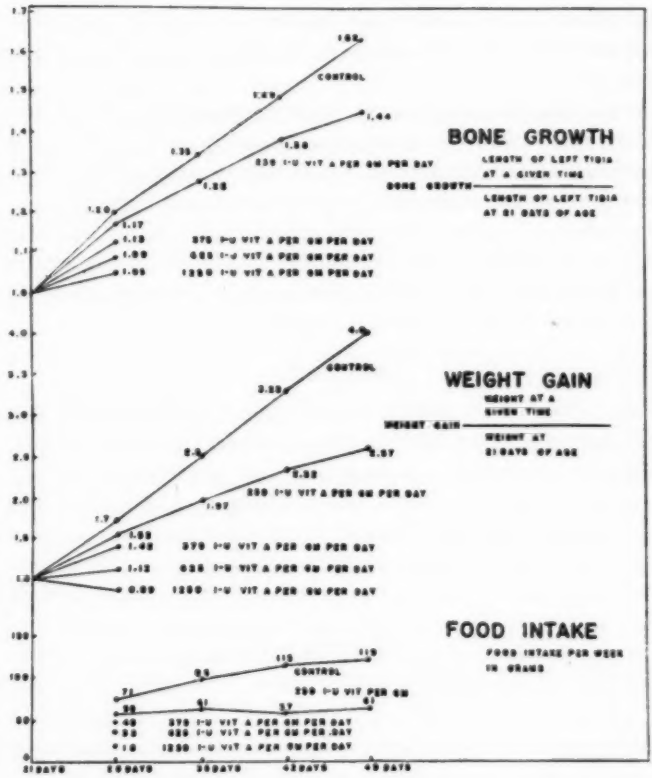

FIG. 3. THE INFLUENCE OF HYPERVITAMINOSIS A ON BONE GROWTH, WEIGHT GAIN AND FOOD INTAKE

Number of Animals

Control: No Vit. A supplement: 16 rats for 1st week 8 thereafter
250 1-U Vit. A per gm. per day: 12 rats for 1st week 8 thereafter
375 1-U Vit. A per gm. per day: 10 rats
625 1-U Vit. A per gm. per day: 16 rats
1250 1-U Vit. A per gm. per day: 16 rats

the more pronounced the effect. These roentgenograms were taken too early to demonstrate fracture. Fracture was always observed, however, across the region of decreased density between the 7th and 14th day of treatment when 625 or 1250 international units of vitamin

A per gram of body weight per day were given, but only after the fourth week of treatment when 250 international units of vitamin A were given.

The microscopic changes were entirely similar to those described by Wolbach (6). Indeed, some of his observations were made on sections taken from these very animals. *The magnitude of change again was directly proportional to the amount of vitamin A administered.*

Coincidental to these gross and microscopic changes, and likewise increasing in degree in direct proportion to the amount of vitamin A given, was retardation of longitudinal growth of the left tibia, weight gain, and food intake as shown in Figure 3.

DISCUSSION

These animals were given a fish oil concentrate containing vitamin A. Under the experimental condition outlined, this distillate produced morphologic changes in the long bones of rats identical with those described by Wolbach (6); morphologic changes which he has produced using crystalline vitamin A as well as a similar distillate; morphologic changes which are therefore almost surely specific manifestations of hypervitaminosis A. It is felt in agreement with Wolbach and for the reasons which he advances that these morphologic changes may be interpreted as due to the acceleration of normal processes; to wit, the acceleration of maturation, degeneration, and death of epiphyseal cartilage cells, replacement bone formation, and the acceleration of normal remodelling of the bone. These morphologic changes may be produced by all of the dosages of vitamin A administered, but are the more pronounced the larger the dose of vitamin A given. Coincidental with these morphologic changes and again proportional to the amount of vitamin A given is a retardation of longitudinal bone growth. Therefore, in hypervitaminosis A, those bones that elongate most slowly because of larger doses, remodel most quickly. Accelerated longitudinal growth is therefore not the factor that makes these bones remodel more rapidly than normal bones. It seems likely, therefore, as Wolbach has already suggested (6), that some factor other than stress and strain must be important in the rapid remodelling seen in hypervitaminosis A.

These experiments establish the fact that in hypervitaminosis A longitudinal growth of long bones is retarded. They do not explain

why this phenomenon occurs. The reduction in food intake, which so closely parallels the reduction of bone growth and similarly is proportional to the amount of vitamin A given, may be one factor responsible. The proportional diminution in weight gain suggests that this retardation of growth may apply to tissues other than bone. The mechanism of growth retardation and the extent of its influence in hypervitaminosis A warrant further investigation.

CONCLUSIONS

Under the experimental conditions outlined, it has been demonstrated that:

(1) Hypervitaminosis A produced accelerated remodelling of the tibia of the growing "weanling" rat. This acceleration was proportional to the amount of vitamin A given.

(2) Hypervitaminosis A in the same animals produced retardation of longitudinal growth of the tibia. This retardation was proportional to the amount of vitamin A given.

It is, therefore, possible to have accelerated remodelling of bone that is secondary to no readily appreciable increase in the stress and strain operating in and on that bone.

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EXPERIMENTAL ANAPHYLACTIC LESIONS OF THE CORONARY ARTERIES OF THE "SCLEROTIC" TYPE, COMMONLY ASSOCIATED WITH RHEUMATIC FEVER AND DISSEMINATED LUPUS ERYTHEMATOSUS

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It has been recognized for many years that narrowing of the branches of the coronary arteries as a result of intimal proliferation occurs commonly in rheumatic fever. This lesion, in its more advanced and fibrous form, often closely resembles and, indeed, may become indistinguishable from ordinary arteriosclerosis. In earlier stages, however, the lesions are usually distinguishable from ordinary arteriosclerosis by their inflammatory component. The inflammation may be confined to the intima, or it may involve the entire vessel wall. Focal necrosis of the media is frequent, and well-marked early lesions of this type have the necrotizing-inflammatory characteristics of periarteritis nodosa. This was pointed out years ago by Aschoff (1) in his original paper on rheumatic carditis, and has been confirmed repeatedly. The healing of such lesions may leave only a thickened, fibrous intima, or there also may be focal scars in the media if medial necrosis has occurred. These various lesions of the coronary arteries, which occur with great frequency in rheumatic fever, have been well described by Perry (2), Klinge (3), Karsner and Bayless (4), Coombs (5), Gross, Kugel and Epstein (6), and others, and they are familiar to all students of the pathology of rheumatic fever.

It is well known that intimal proliferation occurs in periarteritis nodosa, and that in older lesions the thickened intima becomes fibrous, permanently narrowing the lumen of the vessel. That periarteritis nodosa in man can result from protracted hypersensitive reactions of the anaphylactic type has been shown by one of us (8) (9) (10), and we have demonstrated that this vascular lesion can be produced experi-

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mentally by subjecting animals to anaphylactic reactions of the serum sickness type (11). In the report of those experiments, we drew attention to the fact that the lumen of some of the affected arteries became narrowed as a result of intimal proliferation. We have also shown experimentally that valvular, endocardial and myocardial lesions with the basic characteristics of rheumatic carditis can be caused by protracted hypersensitive reactions of the anaphylactic type (12). Hopps and Wissler (13), Hawn and Janeway (17), and Crockett and Roberts (7) have confirmed these experimental results. In other studies we have pointed out that alveolar capillary damage and thrombosis, of the type that characterizes rheumatic pneumonitis, can result in man from anaphylactic hypersensitive reactions to drugs (14), and can occur during protracted anaphylactic reactions in experimental animals (15). We have presented still other forms of evidence in support of the view that the lesions of rheumatic fever, in whatever tissue they are found, may represent effects of an antigen-antibody reaction such as that which occurs in protracted hypersensitive reactions of the anaphylactic type (12) (18). The present observations add to the previously accumulated evidence the fact that the familiar "rheumatic coronary sclerosis" can, likewise, result from protracted anaphylactic reactions to foreign antigens.

This study comprises 45 rabbits which were sensitized to horse serum in a manner that is known to be favorable to the production of the serum sickness type of protracted anaphylactic reaction both in man and in the rabbit, namely, the intravenous injection of large amounts of the antigen. Male albino rabbits, averaging about 2 kg. in weight were used. Sterile horse serum without preservative[2] was injected into the ear vein in a dosage of 10 cc. to 15 cc. per kilogram. Seven of the forty-five animals received only a single injection; twenty-five received two injections, and thirteen received five to ten injections at various intervals. The animals were killed at periods between 17 and 364 days following the first injection of serum, and the coronary arteries were carefully studied microscopically in appropriate sections of the heart. The vessels in most of the other viscera were similarly studied.

[2] The serum was kindly provided by the Medical-Research Division of Sharp and Dohme, Inc.

All of the forty five animals became skin sensitive. Eight responded to the intracutaneous injection of 0.1 cc. of horse serum on the flank, with a severe Arthus phenomenon, i.e., edema, erythema, haemorrhage, necrosis and ulceration; fourteen with edema and haemorrhage; nineteen with an area of edema and erythema four centimeters in diameter or larger; and four with an area of edema and erythema less than four centimeters in diameter. All of the animals in which lesions of the coronary arteries were found at autopsy had developed the serum sickness type of reaction (fever, erythema) following one or more of the intravenous injections of serum, but arterial lesions were not found in all animals which had exhibited this type of reaction.

Eighteen of the forty-five sensitized rabbits developed lesions of the coronary arteries of the type familiar in rheumatic fever. All stages and degrees of this vascular alteration were encountered. Figs. 1 through 13 illustrate the more advanced forms in comparison with examples of human "rheumatic coronary sclerosis." Three of the eighteen animals that developed the coronary lesions had received only one injection of horse serum; thirteen had received two injections; one had received five and one nine injections. All except two of the sensitized animals in which the vascular lesions were found were killed between nineteen and forty-six days after the first injection of serum.

We have not observed lesions of this type in the coronary arteries of non-sensitized rabbits used in this laboratory in other connections. During the course of these experiments a group of eighteen male albino rabbits, weighing approximately 2000 gms. each, were kept as controls in the same room under identical conditions of housing and diet. They received no serum. These controls were allowed to live from 86 to 134 days, i.e. they remained in the laboratory two to seven times as long as most of the sensitized animals that developed the vascular lesions. No lesion of the coronary arteries was found in any of these control animals.

Fibrotic intimal lesions, similar to those occurring in the coronary arteries, were found in peripheral arteries (thymus, epididymis, mesentery) of some of the sensitized animals. It may be noted that fibrotic narrowing of the lumen of small branches of the hepatic artery that are embedded in the scars of lesions produced by coccidia in the rabbit's

liver may be encountered in control animals, and bear no relation to sensitizing procedures. The "sclerosis" of a branch of the hepatic artery regarded by Sato (16) as a result of the injection of foreign protein appears to be a lesion resulting from coccidiosis, for the illustrated narrowed artery is embedded in a scar of the coccidiosis type.

One of us (18) has recently pointed out that disseminated lupus erythematosus exhibits, in common with rheumatic fever and periarteritis nodosa, an impressive variety of lesions, each of which occurs in protracted anaphylactic reactions of the serum sickness type, namely, fever, urticarial and erythematous cutaneous eruptions, purpura, arthritis, necrotizing-inflammatory arterial lesions, focal collagen degeneration, focal necroses of lymph nodes and of spleen, myocarditis, valvulitis, sterile inflammation of serous membranes, sterile pneumonitis, transient paresis. It is of no little interest, therefore, that in disseminated lupus erythematosus there occur "sclerotic" lesions of the coronary arteries of the same type as those that occur in rheumatic fever, in periarteritis nodosa and in our animals subjected to experimental serum sickness. That these lesions are related to disseminated lupus itself, and are not coincidental arteriosclerotic lesions, is evident from the fact that they occur even in children with the disease. Figures 14 and 15 illustrate lesions of this type in a child 11 years old, who had typical clinical and pathological disseminated lupus erythematosus.

SUMMARY

Lesions of the coronary arteries, altogether comparable with the "sclerosis" of the branches of the coronary arteries caused by rheumatic fever, ocurred in 18 of 45 rabbits subjected to protracted anaphylactic reactions of the serum sickness type, and were not found in control rabbits. This observation adds further evidence to that which we have previously presented in support of the view that the various lesions of rheumatic fever can result from antigen-antibody reactions of the anaphylactic type.

In disseminated lupus erythematosus, also, coronary "sclerosis" of the same type occurs, and a wide variety of other lesions that are characteristic of protracted anaphylactic reactions.

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EXPLANATION OF ILLUSTRATIONS

(Photomicrographs by Miss Marjorie Jackson)

FIG. 1. Branch of coronary artery from a case of rheumatic fever in a 5 year old child, with Aschoff bodies in myocardium (Autopsy 13, 551).

FIG. 2. Branch of coronary artery from rabbit (63), which had received 2 injections of horse serum, 10 cc./kg. each, and was killed 28 days after the first injection.

FIG. 3. Branch of coronary artery from a case of rheumatic fever in a male 24 years old, with Aschoff bodies in myocardium (Autopsy 18, 556).

FIG. 4. Branch of coronary artery from same case as Fig. 1.

FIG. 5. Branch of coronary artery from rabbit (64), which had received 2 injections of horse serum, 10 cc./kg. each, and was killed 28 days after the first injection.

FIG. 6. Branch of coronary artery from a case of rheumatic fever in a child 6½ years old, with Aschoff bodies in myocardium (Autopsy 7814).

FIG. 7. Branch of coronary artery from rabbit (83), which had received 9 injections of horse serum, 10 cc./kg. each, during 260 days.

FIG. 8. Branch of coronary artery from case of rheumatic fever in a youth 17 years old, with Aschoff bodies in myocardium (Autopsy 9181).

FIG. 9. Branch of coronary artery from rabbit (87), which had received 5 injections of horse serum, 10 cc./kg. each, during 122 days.

FIG. 10. Branch of coronary artery from rabbit (7), which had received 10 cc./kg. of horse serum and was killed 28 days later.

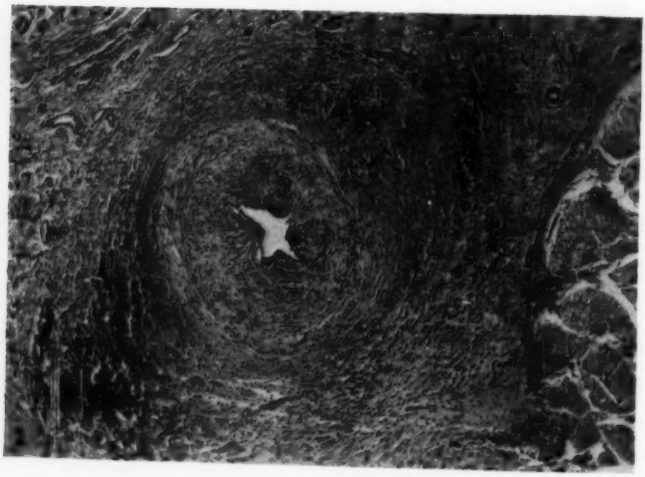
FIG. 11. Branch of coronary artery from rabbit (8), which had received 2 injections of horse serum, 10 cc./kg. each, and was killed 26 days after the first injection.

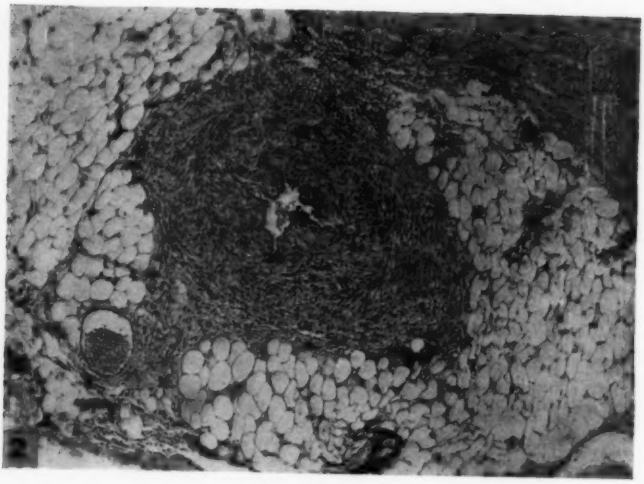
FIG. 12. Larger branch of coronary artery from same case of rheumatic fever as Fig. 8. The position of the internal elastic membrane is outlined with ink.

FIG. 13. Larger branch of coronary artery from rabbit (65), which had received 2 injections of horse serum, 10 cc./kg. each, and was killed 28 days after the first injection. The position of the internal elastic membrane is outlined with ink.

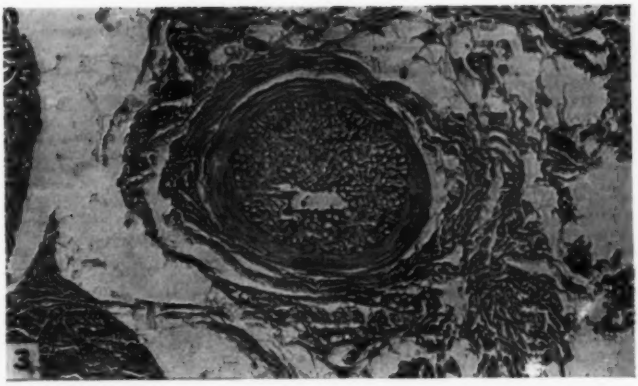
FIG. 14. Branch of coronary artery from a case of disseminated lupus erythematosus in a child 11 years old (Autopsy 20,354). Compare with Figs. 3, 4 and 5.

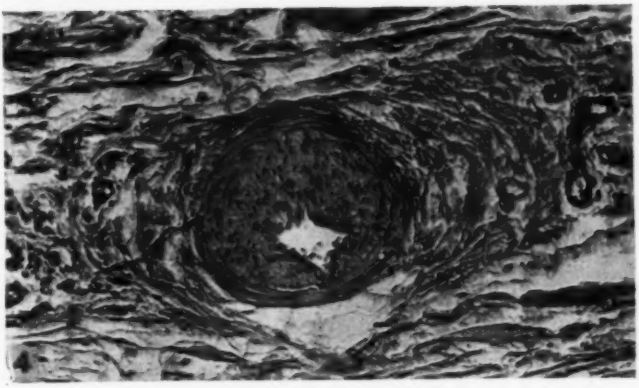
FIG. 15. Larger branch of coronary artery from same case of disseminated lupus erythematosus as in Fig. 14. The position of the internal elastic membrane is outlined with ink. Compare with Figs. 12 and 13.

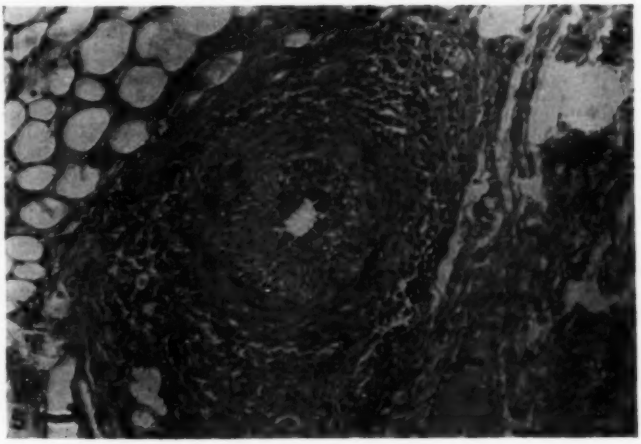




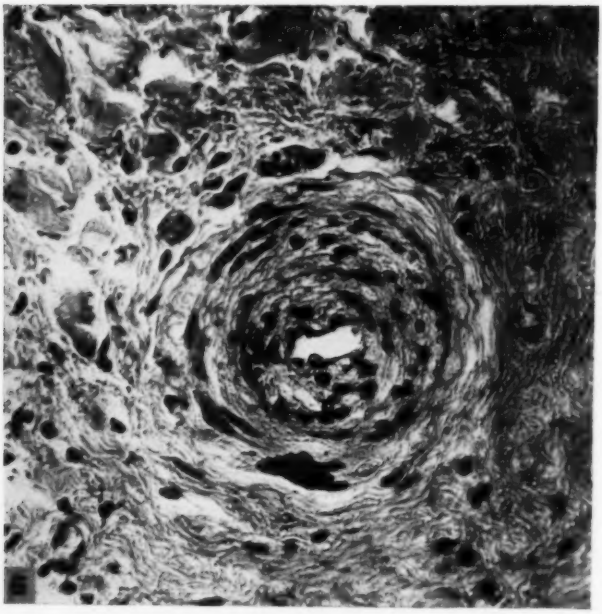
FIGS. 1 AND 2

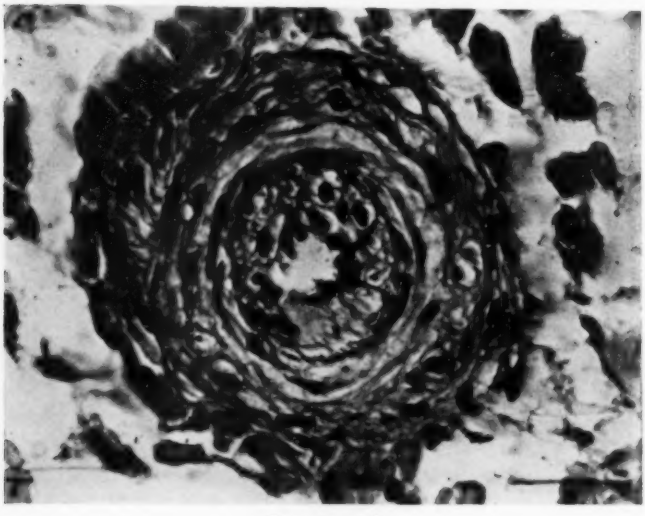




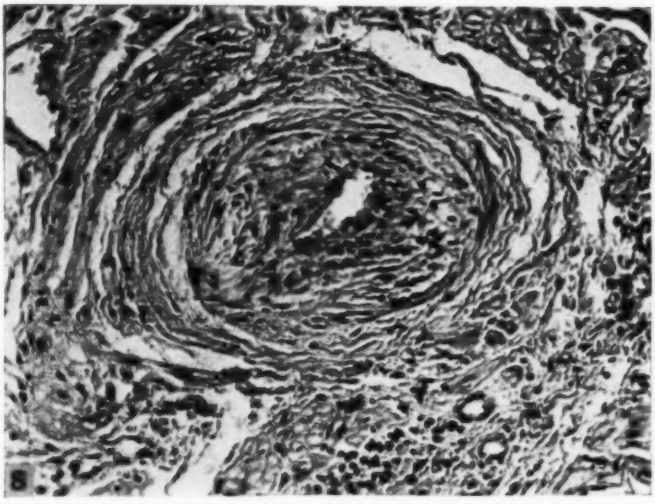


FIGS. 3, 4 AND 5

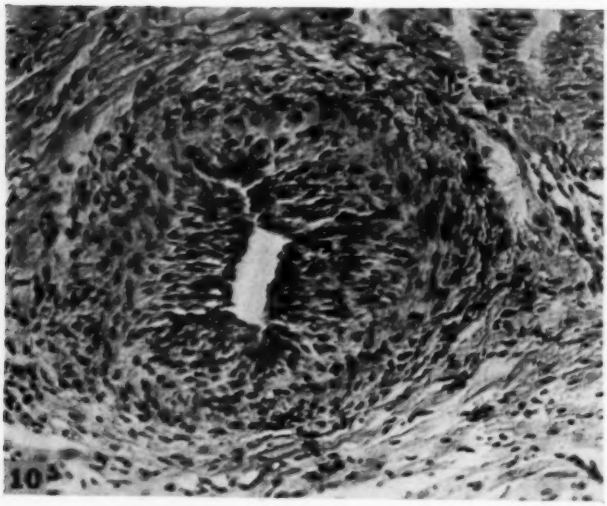


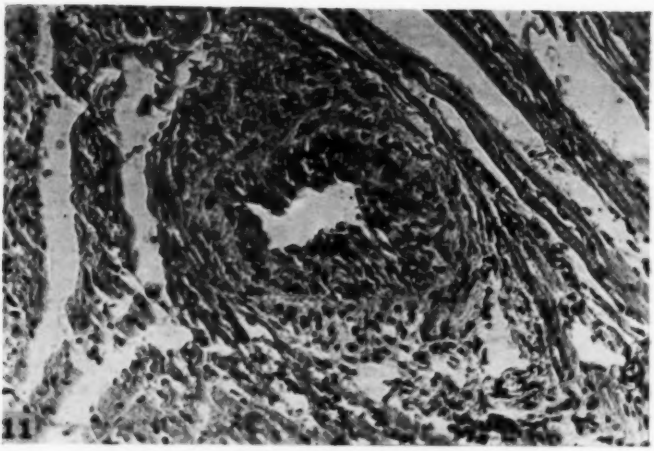


FIGS. 6 AND 7

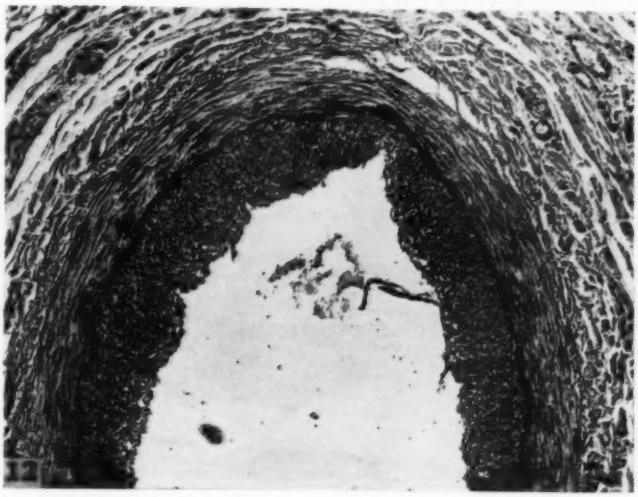


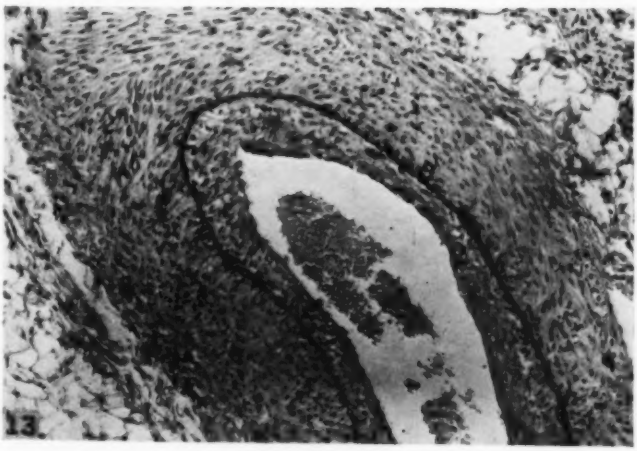
FIGS. 8 AND 9



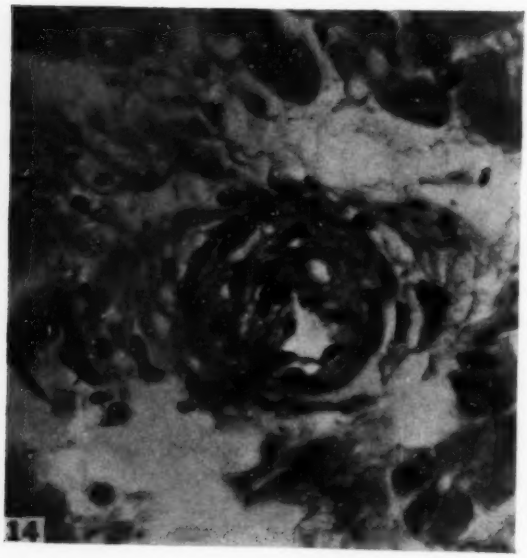


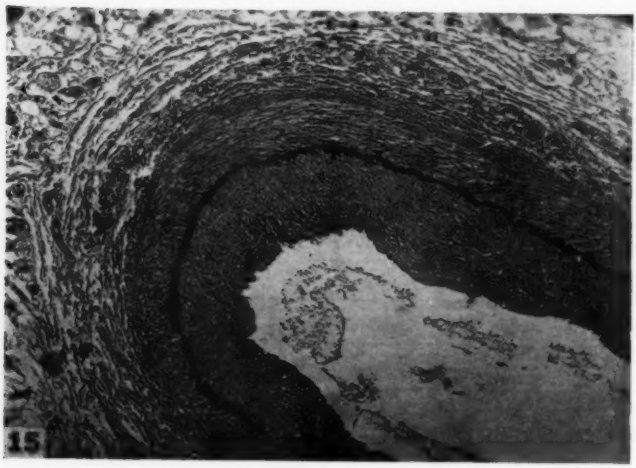
FIGS. 10 AND 11





FIGS. 12 AND 13





FIGS. 14 AND 15

OBSERVATIONS ON AN EPIDEMIC OF INFLUENZA B OCCURRING AT THE JOHNS HOPKINS HOSPITAL IN NOVEMBER–DECEMBER, 1945[1]

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During November and December, 1945, an outbreak of respiratory disease, shown to be influenza type B, occurred among personnel of the Johns Hopkins Hospital concomitantly with other localized outbreaks in both civilian and military groups widely dispersed in the United States, Pacific Ocean, Alaska and the Antilles (1). This report is based on clinical observations made at the time of the local epidemic and on subsequent laboratory studies of specimens collected from hospital personnel ill with influenza during this period.

CLINICAL DATA

Sources of material: The group studied includes approximately 600 nurses and dieticians at the Johns Hopkins Hospital, predominantly students. Student nurses are required to report at the onset of any illness to the infirmary where medical service, including hospitalization, is provided. One of the authors (G.R.L.) was personally responsible for the medical care of the group.

Incidence: In this group, the epidemic began apparently during the last days of November, 1945, as the onset of the first proved case was November 30. The outbreak reached its maximum by the second week in December, and waned rapidly thereafter. (See Table 1.)

The last two proved cases of influenza "B" began on December 26; several subsequent clinical cases showed no increase of antibodies to either influenza "A" or "B". An estimated 15% of the student nurses were hospitalized with clinical influenza during December.

Symptoms: The clinical characteristics of the disease were essentially the same as previously described (2, 3). Clinical data are derived

[1] Supported in part by a grant from the Research Grants Division, National Institute of Health, United States Public Health Service.

[2] From the Department of Bacteriology, School of Hygiene and Public Health, and the Department of Medicine, School of Medicine, The Johns Hopkins University, Baltimore, Maryland.

from 82 cases occurring during November and December, of which 68% of those tested (48 of 71 cases) gave serological evidences of infection with influenza type B.

The mildest symptoms were those of a common cold. The most severe symptoms included prostration, fever sustained at 103–104°F for three or more days, and a prolonged convalescence.

About one-half of the patients described their illness as abrupt in onset, beginning unexpectedly with chilly sensations, or feverishness, shortly followed by prostration, headache, cough, and generalized myalgia. In this group, such upper respiratory symptoms as sore throat, coryza, and nasal congestion appeared late. In the other half, the onset was gradual. Local upper respiratory symptoms predominated.

TABLE 1

Incidence of clinical cases of influenza by date of onset among student nurses and dietitians at The Johns Hopkins Hospital

WEEK ENDING	NUMBER OF CASES	PER CENT DISTRIBUTION
12/3	6	7.3
12/10	35	42.7
12/17	21	25.6
12/24	15	18.3
12/31	5	6.1
Total	82	100.0

Systemic manifestations appeared only after several days, and resulted in the seeking of medical attention. At the height of the disease, prostration, anorexia, generalized headache, backache, and often aching of all extremities were common in both groups.

Pain back of the eyes, and especially pain on motion of the eyes was commonly described. Photophobia occurred rarely. The throat was described as "dry and scratchy," rather than painful. Cough was common at some stage of the illness, tended to appear late, and was persistent.

Physical examination: Few physical abnormalities other than the flushed face, conjunctival injection and pharyngitis were noted. The

oropharyx was remarkably uniform in appearance. It was dull red in color, dry and granular, with loss of the sheen of normal mucous membranes and without exudate or edema. The smaller blood vessels of the soft palate and uvula were often dilated and prominent.

In 8 cases which were shown by serological tests to be influenza Type B, roentgenograms of the chest were taken during the acute stage of the illness. No evidence of pathological changes due to influenza were noted.

Course of the disease: The patients were hospitalized as a rule until they had been afebrile for 48 hours, or until they were asymptomatic. The average duration of fever was two and eight-tenths days, of hospital stay, four and eight-tenths days. Weakness, anorexia, and cough

TABLE 2

Bacteriological Data

Throat and Nasopharyngeal Cultures	
Normal Flora	48
Possible pathogens predominant	12
Staph. aureus	4
Str. hemolyticus	1
D. pneumoniae	3
H. influenzae	2
Staph. aureus & Str. hem.	1
Staph. aureus & D. pneumoniae	1
Total	60

were the most persistent of the symptoms, often continuing many days after the temperature had returned to normal. The average loss of working time, including hospitalization, was eight days.

There were no serious complications and no deaths.

Clinical pathology: Of 60 throat and nasopharyngeal cultures, 48 yielded normal throat organisms in the usual proportion, and 12 yielded a variety of possible pathogens. In no case did these organisms appear to have any relationship to the cause or severity of the illness.

Leucocyte counts were in the low normal range. Of 32 determinations, the lowest was 3400, the highest 9400, and 75% were between 4800 and 7000 white blood cells per cubic millimeter of blood. The bacteriological data are presented in Table 2.

LABORATORY INVESTIGATIONS

Isolation of virus: A total of 38 throat washings was obtained, nine of which were collected during the first 24 hours of disease. The patient was requested to gargle with two or three 5 ml. of a 50% infusion broth-normal saline mixture, which was stored in sterile test tubes at −20°C. until tested.

Fertile White Leghorn eggs, incubated at 38.5°C. for 13 days, were inoculated intra-amniotically (6) with 0.4 ml. of unfiltered throat washings containing approximately 200 units of penicillin per milliliter. The inoculated embryos were incubated at 35°C. for 4 days at which time the amniotic fluids were harvested.

These amniotic fluids were tested for the presence of virus by hemagglutination of erythrocytes, using the Salk technic (4). Each amniotic fluid was tested in final dilutions of 1/16, 1/32 and 1/64 in physiological saline, using equal volumes of amniotic fluid dilution and 0.5% washed, normal chicken erythrocytes and 0.7% washed normal guinea pig erythrocytes.

Lungs and tracheas of embryos yielding negative fluids were removed, ground with alundum, and resuspended in the amniotic fluids of the same embryos. This material was used for the next passage. Six passages were made before a specimen was considered negative.

Amniotic fluids shown to contain virus were inoculated into the allantoic sac of 11 day-old embryos and incubated at 35°C. for 48 hours. The embryos were chilled overnight at 4°C. to prevent bleeding. The allantoic fluids were harvested and the viruses were identified by the hemagglutination-inhibition test using known immune serum. Using this technic, 8 strains of influenza "B" virus were isolated from the 38 throat washings collected from nurses and dieticians ill with influenza in late 1945.

Table 3 indicates the day of disease on which the throat washing was collected and the number of specimens from which virus was isolated.

While the numbers in the table are small and no conclusive results may be drawn from them, there is an indication that, using the technic described, virus may be isolated more readily during the first 3 days of disease than at later stages.

Serological studies: Two sera from each patient were tested for

change of antibody titre to influenza A and B. The first serum was collected as early in the disease as was feasible, the second usually from 10 days to 5 weeks later. Sera were stored at −20°C. until used. Both sera from each patient were always tested at the same time.

The method used in detecting a rise in antibodies was the chick cell agglutination-inhibition test, performed essentially as described by Hirst (5). It was simplified by performing the serial dilutions of serum in chicken erythrocyte suspensions, rather than in saline, thus eliminating one step in the procedure. In order to have the same final concentration of erythrocytes in each tube, it is necessary to use a 3% red blood cell suspension in the first tube of each series, and 1.5% suspen-

TABLE 3

Frequency of virus isolation by day of disease

DAY OF DISEASE	NUMBER COLLECTED	THROAT WASHINGS NUMBER POSITIVE
1	9	2
2	8	3
3	12	2
4	3	0
5	3	1
6	0	0
7	1	0
Undetermined	2	0
Total	38	8

sions in all others. Agglutination tests were done in tubes 9 mm in diameter. The test was read at the end of 75 minutes, and the endpoint determined as the highest dilution of serum which showed 50% or less sedimentation of erythrocytes as compared with a control erythrocyte suspension in saline. Only a rise in antibody titre of at least 4-fold (two tubes) was considered significant. Positive virus and negative serum controls were included in each test.

Virus suspensions were obtained by the intra-allantoic inoculation of 11 or 12-day old chick embryos, using egg adapted PR8 strain of influenza type A virus, and Lee strain of B type virus[3]. The allantoic fluid was harvested after 48 hours incubation and used without further

[3] The authors are indebted to Dr. Thomas Francis, Jr. for strains of these viruses.

treatment. Later, a supply of virus of the same strains, purified by Sharpless centrifugation was used[4]. Four agglutinating units of virus per tube were used routinely in the test (5).

Results: Paired sera from 71 patients on whom the diagnosis of influenza was made during November and December, 1945, were tested. Forty-eight (68%) had a 4-fold or greater rise of antibodies to influenza type B and 10 more had a 2-fold rise to influenza type B. None showed more than a 2-fold rise to influenza type A. (See Table 4.)

TABLE 4

Serum antibody rises of paired sera of patients with clinical influenza, November–December, 1945

RISE IN TITER	NO. OF PAIRS OF SERA	PER CENT DISTRIBUTION
None	13	18.3
2-fold	10	14.1
4-fold	26	36.6
8-fold	8	11.2
16-fold	7	9.9
>16-fold	7	9.9
Total	71	100.0

TABLE 5

Serum antibody levels of patients from whom Influenza virus was isolated

ACUTE SERUM LEVEL*	CONVALESCENT SERUM LEVEL*	RISE IN TITER
40	160	4-fold
80	160	2-fold
80	320	4-fold
80	320	4-fold
80	2560	32-fold
160	1280	8-fold
160	640	4-fold
No serum	—	—

The relation of serum antibody to virus isolation may be seen in Table 5.

*Titers expressed as reciprocals of final dilution.

Table 5 warrants no definite conclusions because of the small number of positive specimens.

[4] Dr. Harold E. Cox kindly furnished this material.

Of the 7 patients with positive throat washings whose corresponding paired sera could be tested, 6 (86%) showed a 4-fold or greater rise of antibodies during convalescence. Of 28 patients with negative throat washings, 20 (71%) showed a similar rise of antibodies.

DISCUSSION

Epidemic influenza, type B, appeared in Baltimore during the winter of 1945–46. The occurrence of influenza among the personnel of The Johns Hopkins Hospital afforded the opportunity to make the observations recorded in this paper.

The disease, as observed, was moderately severe, with the usual clinical characteristics. The epidemic was of abrupt onset, and a somewhat more gradual decline. Laboratory evidence, afforded by virus isolations and serological studies, indicated that the epidemic of influenza type B ceased abruptly about four weeks after the onset. Clinically, respiratory disease indistinguishable from influenza occurred with unexpected frequency for at least two more weeks. There is no evidence available which would indicate the etiology of these cases, or of the cases occurring during the epidemic which showed no rise of antibodies to influenza type A or B.

Influenza B virus was isolated 8 times from 38 throat washings. Of the 38 patients whose throat washings were tested, and whose sera were titered for influenza type B antibodies, 26 showed a 4-fold rise in antibodies, and thus almost certainly had influenza. Presumably they harbored the virus in their respiratory tract at some time during the illness. Of these 26 throat washings 6 yielded virus, or 23%. This percentage could perhaps be improved by using combined nasal and throat washings. Possibly virus isolation can be accomplished with regularity only during the earliest days of the illness. In this study, only one strain was isolated later than the 3d day of disease.

There seems to be no correlation between frequency of virus isolation and either (1) serum antibody level at the time the throat washing was taken, or (2) subsequent rise of antibody to influenza.

The virus strains which have been isolated have not been studied intensively. However, it is apparent that they differ in several aspects from the Lee strain of influenza type B. Hemagglutination titers are lower and tend to diminish with chick embryo passage. Repeated attempts to adapt representative strains to white mice have been un-

successful. However, by serological methods these strains have been shown to be closely related to the Lee strain of influenza type B.

CONCLUSION

Summary: 1. Epidemic influenza type B was prevalent among the nurses and dieticians of The Johns Hopkins Hospital during November and December, 1945. The clinical and laboratory manifestations of the disease among that group are presented. 2. The disease was mild, and involved about 15% of the group. There were no deaths, and no serious complications. The average duration of fever was two and eight-tenths days; of hospital stay, four and eight-tenths days; and of time lost from duty, eight days. 3. Influenza type B virus was isolated from throat washings of 8 of 38 patients by intra-amniotic inoculation of 13 day old chick embryos. 4. Forty-eight of 71 pairs of sera from patients ill with influenza during December, 1945, showed a significant (4-fold) rise of antibodies to influenza type B virus. None showed a significant rise to type A virus.

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UNUSUAL PATHOGENICITY OF PASTEURELLA MULTOCIDA ISOLATED FROM THE THROATS OF COMMON WILD RATS[1]

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Our first discovery, that Pasteurella multocida is present in the throat of the wild Norway rat, was accidental. When looking for pneumococcus carriers (1), we repeatedly isolated from throat-swabs of wild Norway rats a small, Gram-negative, non-motile rod, which grew well on plain agar, and showed bi-polar staining with Methylene blue. It was finally identified by us, and confirmed by the National Institute of Health, as one of the species of *Pasteurella multocida*.[2] Subsequently, a study was made of the throat-swabs of 102 wild Norway rats caught in the city of Baltimore, and 14 strains of this micro-organism were isolated from 14 different rats.

Since there is no report in the literature of *Pasteurella multocida* being carried in the throats of wild rats, a detailed study of animal pathogenicity, biology, serology, and penicillin sensitivity of the strains was made.

P. multocida (sometimes called *P. septica*) has long been held responsible for epidemics of hemorrhagic septicemia in a large variety of animals. The animal pathologist has reported many outbreaks of this disease in horses, cattle, sheep, reindeer, swine, cats, ducks, chickens, rabbits, and mice; all were highly fatal and of short duration. Farmers have named the disease "shipping fever" because of frequent occurrence during transportation of animals. Only one report of hemorrhagic septicemia among wild rats was found. This was an outbreak in the wild rats of Oakland, California, studied in detail by Karl F. Meyer et al. (2). However, in this excellent study, no cross-

[1] This work was supported by a grant from the Dazian Foundation for Medical Research.

[2] We are indebted to Dr. C. L. Larsen for carrying out these tests.

agglutination or cross-pathogenicity tests with other known *Pasteurella multocida* strains were reported.

Moore, in 1895 (3), isolated *P. multocida* from the mucous membranes of the respiratory tract of apparently normal cattle, sheep, swine, dogs, and cats. More recently, Schenk (4) studied in detail strains of *P. multocida* recovered from apparently normal and sick cats, some of which had infected human beings.

Human infections, which have been reported seldom, but are being more often recognized, can be divided into two types. The first type is caused by animal bite, resulting in a local infection, with now and then generalized symptoms. Many cat bites (5, 6, 7, 8, 9, 10), one panther bite (11), one rabbit bite (12), and some dog bites (8) have been reported as causing this type of infection.

The second type of infection has not been connected with any known, direct cause. It may present a wide variety of clinical symptoms, ranging from long standing recurrent chills and fever to isolated cases of pleuritis and meningitis. Such infections have been reported mainly in Europe (13), and never in the United States.

The large group of Pasteurella organisms, causing hemorrhagic septicemia in animals, has been divided into various species, according to the animal from which each was isolated. Thus various names as *P. avicida*, *P. boviseptica*, *P. suiseptica*, *P. lepiseptica* have been used. Evidence has been accumulating that this zoological classification is meaningless since cross-pathogenicity tests and cross-agglutination tests by many workers (14, 15, 16), as well as cultural and biochemical similarities, showed that all the strains isolated from different animal species were nearly identical. Recently, Rosenbusch and Merchant (17) studied extensively 114 strains from many different animals and could not differentiate the strains by serological tests. Therefore, the name proposed by Kitt in 1895, *P. multocida*, has been adopted for all animal strains.

EXPERIMENTAL

Isolation of Strains of Pasteurella Multocida

The 102 wild Norway rats used for the isolation of the 14 recovered Pasteurella strains were made available to us by Dr. Curt P. Richter of the Psychobiological Laboratory of the Johns Hopkins Hospital. They were trapped in different parts of the City of Baltimore, Mary-

land, and at the time of throat-swabbing had not been held longer than 4 days in the laboratory. With the aid of the wiresock, first described by Emlen (18), these wild rats could be handled very easily. After the rat had been secured in a sock, the upper and lower incisors were held apart by the loop of the end of a wire brush handle. A cotton swab was then easily inserted into the pharynx.

Every throat-swab was placed immediately into about 2 cc. of beef infusion broth and used the same day for plating on rabbit-blood-agar and for injection of 0.25 cc. intraperitoneally into one adult Swiss mouse. The remainder of each specimen was kept in a dry ice box at −78°C. for later studies.

Every rabbit blood agar-plate was incubated at 37°C. for about 20 hours, and a colony, morphologically suggestive of *P. multocida*, was picked in beef infusion-broth and further biochemical studies were made. Diphtheroids, streptococci and proteus were abundant on the blood plates.

From every mouse which died within 4 days after inoculation, a culture of the tailblood and peritoneal exudate was taken. All mice dying within that period yielded pure cultures of *P. multocida*, except three from which pure cultures of streptococci were obtained and an additional five from which mixed cultures of proteus and suggestive pasteurella were obtained. Repeated attempts to get rid of proteus by intraperitoneal mouse-inoculations failed.

A total of 14 strains were isolated by the biological method of mouse-inoculation and could also be identified morphologically on the blood plate cultures of the original throat-swabs. Their similarity by other biochemical tests was later established.

Several blood plate cultures from throat swabs which did not kill mice yielded strains suggesting *P. multocida*, but were not used for further studies since they were not virulent for mice.

The 14 strains isolated from 102 rats and used for further study in this work were, therefore, specific mouse-virulent strains and did not necessarily represent the true percentage of carriers of *P. multocida* in the rats. Moreover, five strains isolated from mouse-cultures were overgrown with proteus, as mentioned above, and were discarded.

Twenty original throat-washings, which showed diphtheroids on the blood agar plate, were streaked on Loefflers slants and colonies, suggestive of *C. diphtheriae* picked for growth on tellurite medium.

Colonies on the tellurite medium were selected because of typical metal-like appearance, and three pure cultures were finally selected which were highly suggestive of *C. diphtheriae*. However, subsequent tests in guinea pigs showed them to be avirulent strains.

Animal Pathogenicity

All 14 strains of *P. multocida* were tested for virulence in mice and rabbits, and two of our first isolated strains, WR2b and WR38, were tested in a large number of other animal species.

The pathogenicity of the other 12 strains for mice and rabbits, and of strains WR2b and WR38 for rabbits and other animal species was tested in each case by injecting intraperitoneally 0.5 cc. of a 10^{-2} dilution in beef broth of an 18 hour beef broth culture of the strain. From animals which died, a heart or tail blood culture was taken and only animals with a positive culture were accepted as having succumbed to the inoculum. All but two strains of *P. multocida* included in this study killed mice and rabbits within 24 hours after inoculation.

The virulence of strains WR2b and WR38 was tested in mice by the intraperitoneal injection of 0.5 cc. of serial 10-fold dilutions of an 18 hour broth culture. All mice inoculated with dilutions ranging from 10^{-0} up to 10^{-6} died in 12–24 hours; the mice with the highest dilutions succumbing last.

Inocula of 0.5 cc. of a 10^{-2} 18 hour broth culture of strains WR2b and WR38 were found to kill the following animals within 24 hours after intraperitoneal injection: 2 guinea pigs, 2 hamsters, 4 Cotton rats, 4 Alexander rats, 3 chickens. Strain WR2b was similarly tested in a cat and a dog, and killed each in about 12 hours.

Following subcutaneous inoculation into rabbits, *P. multocida* produced death within 3 to 4 days. On autopsy, characteristic gross lesions were found consisting of serous exudates in the peritoneal, pericardial and pleural cavities and occasional petechial hemorrhages in the lungs.

Having found the unusual virulence of *P. multocida* for many animals, including a dog, the question arose whether a rat, carrying *P. multocida* in his throat, would be able to infect a susceptible animal by biting.

For this purpose a small part of the belly of a dog was shaven, the

skin folded, and two Norway rats, (WR67, 81) carrying *Pasteurella* in the throat were allowed to bite through the skin till some blood appeared. The dog was kept under observation for 14 days but did not show any sign of illness in this time, so observations were discontinued. This forgotten dog, however, was found dead in its cage 23 days after the original rat bites. On autopsy, pathological changes were found only in the lungs, namely, tiny diffusely scattered haemorrhagic areas. The peritoneal cavity appeared normal and no abscesses were found. Cultures were taken from the peritoneum, heart blood and lung. Only the lung culture showed growth, a mixed culture of streptococci and a Gram-negative bipolar rod, which was subsequently identified as *P. multocida*.

To our surprise, Norway rats and hooded or albino rats were found to be resistant even to the intraperitoneal inoculation of 0.5 cc. of undiluted culture. This was confirmed during a six month period of repeated trials on a total number of 16 tame rats and 15 Norway rats, several of the latter carrying *P. multocida* in their throats. Also, intranasal and subcutaneous inoculations on the abdominal wall or at the root of the tail, to which mice were susceptible, did not seem to make the rats sick. All rats were kept under observation for a 20 day period.

To investigate further this non-susceptibility of the Norway rat and the tame rat, a series of four experiments was carried out:

a. Norway rats, Cotton rats, and mice were inoculated intraperitoneally with undiluted 18 hour broth cultures of strains WR38 and WR48, and blood cultures were taken at varying intervals. In Table I it will be seen that the blood cultures from mice and Cotton rats were positive at 4, 6, and 8 hours after inoculation, whereas the cultures from the Norway rats were sterile.

b. The pooled sera of Norway rats carrying *P. multocida* and the pooled sera of Norway rats from which this microorganism was not cultured were tested for agglutinins against strain WR38. The sera was tested both unheated and following inactivation at 56°C. for 30 minutes. As controls, the serum of a normal rabbit and of a rabbit immunized, as described later, against this strain of *P. multocida* were included. Serial twofold dilutions of the sera in physiological saline were made and mixed with an equal volume of the antigen.

The antigen used in this test was a suspension in physiological saline of heat-killed, saline washed, bacterial cells which had been grown in beef broth 24 hours at 37°C. The test was read after incubating the mixture at 41°C. for 24 hours and then keeping it in the icebox at about 4°C. overnight. It will be seen in Table II that no agglutination was produced by the pooled rat sera or the normal rabbit serum

TABLE I

Invasiveness of Pasteurella multocida Strains

SPECIES INOCULATED	PASTEURELLA STRAIN	BLOOD CULTURE AFTER:		
		4 hrs.	6 hrs.	8 hrs.
Mouse	WR38	+	+	+
Mouse	WR48	+	+	+
Norway rat	WR38	−	−	−
Norway rat	WR48	−	−	−
Cotton rat	WR38	+	+	+
Cotton rat	WR48	+	+	+

TABLE II

Agglutination of Pasteurella multocida

SERUM	SERIAL DILUTIONS OF SERUM					
	1/80	1/160	1/320	1/640	1/1280	1/2560 (final)
Carrier-rat pool	−	−	−	−	−	−
Non-carrier rat pool	−	−	−	−	−	−
Immune rabbit	+	+	+	+	+	+
Normal rabbit	−	−	−	−	−	−

+ = agglutination
− = no agglutination

in dilution of 1/80 or greater. Agglutination was observed in the homologous immune rabbit serum in a dilution of 1:2560.

c. Two rats and two mice were simultaneously inoculated intraperitoneally with 0.25 to 0.50 cc. of a 10^{-2} dilution of a 10 hour broth culture of strain WR38. At different intervals after inoculation the peritoneal cavity of each animal was thoroughly washed with 1 to 2 cc. of sterile broth. From each peritoneal washing a smear was

made, stained with Methylene blue, and studied microscopically, for phagocytosis and number of organisms. Each washing was also cultured on rabbit blood agar plates, and studied for growth after 18 hours incubation at 37°C. It will be seen in Table III that 3 hours after inoculation the smears from the rat and mouse peritoneal cavities were indistinguishable. At 10 hours, however, phagocytosis was much more prominent in the case of the rat though the culture was positive for each species. The smear from the rat at 24 hours showed no micro-organisms and cultures were sterile, whereas the mice had succumbed to the infection.

TABLE III

The Fate of Pasteurella multocida in the Peritoneal Cavity of Mice and Rats

HOURS AFTER INTRAPERITONEAL INOCULATIONS	PERITONEAL WASHING OF RAT	PERITONEAL WASHING OF MOUSE
3 hours later	Phagocytosis + Many organisms Culture positive	Phagocytosis + Many organisms Culture positive
10 hours later	Phagocytosis ++ Few organisms Culture positive	Occasional phagocytosis Numerous organisms Culture positive
24 hours later	No organisms observed Culture negative	Mouse dead Smear teaming with organisms, showing nice bipolarity. Culture positive.

d. Serum of three Norway rat carriers of *P. multocida* (WR47, WR48, WR49) was pooled. A separate pool was made of the serum from three other Norway rats from whom the microorganism was not recovered. With these two serum pools, neutralization experiments were carried out in mice. An inoculum of 0.25 cc. of 10^{-5} dilution of an 18 hour broth culture of strain WR48 (10 M.L.D.) was injected subcutaneously into four mice, two of which had received 0.25 cc. of each serum pool intravenously shortly before. All the mice died within 24 hours after inoculation, and *P. multocida* was recovered by culturing the tail blood. This rigorous test then failed to demonstrate any appreciable difference in neutralizing antibody in the two types of rat serum.

Biology

To identify the Pasteurella strains recovered from the throat-swabs of wild Norway rats, a study was made of the morphological and cultural characteristics and the findings were compared with those of

TABLE IV

Biological characteristics of P. multocida strains

P. STRAIN	HOST ORIGIN	HEMOLYSIS OF RABBIT BLOOD	BIPOLARITY	MOTILITY	GROWTH ON POTATO	GROWTH ON DESOXYCHOLATE AGAR	INDOL PRODUCTION	CHANGE OF LITMUS MILK	FERMENTATION REACTION										BILE SOLUBILITY	MOUSE PATHOGENICITY	RABBIT PATHOGENICITY	ROSENBUSCH-MERCHANT GROUPS
									CATALASE	LACTOSE	DEXTROSE	SUCROSE	LEVULOSE	SORBITOL	GALACTOSE	RAFFINOSE	ARABINOSE	DULCITOL	XYLOSE	MALTOSE				
WR2b	Rat	−	+	−	−	−	+	−	+	−	+	+	+	0	0	0	0	0	0	0	−	+	+	
WR3b	Rat	−	+	−	−	−	+	−	+	−	+	+	+	0	0	0	0	0	0	0	−	+	+	
WR7	Rat	−	±	−	−	−	+	−	+	−	+	+	+	+	+	−	+	−	−	−	−	+	+	I
WR9	Rat	−	±	−	−	−	+	−	+	−	+	−	+	+	+	−	+	−	−	−	−	+	+	I
WR11	Rat	−	±	−	−	−	+	−	+	−	+	+	+	+	+	−	+	+	−	−	−	+	+	I
WR25	Rat	−	±	−	−	−	+	−	+	−	+	−	+	+	+	−	+	−	−	−	−	+	+	I
WR37	Rat	−	±	−	−	−	+	−	+	−	+	+	+	+	+	−	±	−	+	±	−	+	+	?
WR38	Rat	−	+	−	−	−	+	−	+	−	+	+	+	±	+	−	±	−	+	−	−	+	+	?
WR45	Rat	−	+	−	−	−	+	−	+	−	+	−	+	+	+	−	+	−	+	−	−	+	+	?
WR47	Rat	−	+	−	−	−	+	−	+	−	−	+	+	+	+	−	−	−	±	−	−	+	+	II
WR48	Rat	−	±	−	−	−	+	−	+	−	+	+	+	±	+	−	−	−	−	+	−	+	+	?
WR49	Rat	−	±	−	−	−	+	−	+	−	+	−	+	+	+	−	+	−	−	−	−	+	+	I
WR67	Rat	−	+	−	−	−	+	−	+	−	+	+	+	+	+	−	+	−	+	−	−	+	+	?
WR81	Rat	−	±	−	−	−	+	−	+	−	+	−	+	+	+	−	+	−	+	−	−	+	+	?
RT I	Rabbit	−	±	−	−	−	+	−	+	−	+	+	+	−	+	−	−	−	+	−	−	+	+	II
Fl I	Fowl	−	±	−	−	−	+	−	+	−	+	−	+	+	+	−	+	−	−	−	−	+	+	I
Ct I	Cat	−	±	−	−	−	+	−	+	−	+	+	+	+	+	−	−	−	+	±	−	−	−	II
PM195	Cow	+	±	−	−	−	+	+	+	+	+	+	+	+	+	−	+	−	−	+	−	−	0	P. hemolytica
JSB I	Sheep	−	+	−	−	−	+	−	+	−	+	+	+	+	+	−	−	−	+	−	−	+	0	II

0 = Not done.
− = Negative
+ = Positive or acid.

Pasteurella strains recovered from different animal species. The results of all the following tests are shown in Table IV.

Strains of Pasteurella: Strain Ct. I was isolated from the throat of a wild cat, caught by Dr. D. Davis of the Department of Rat Ecology, of the Johns Hopkins School of Hygiene; the animal was known to feed on wild rats. Strains Rt. I and Fl. I were kindly given us by

members of the Department of Bacteriology of the Johns Hopkins School of Medicine. Finally, Dr. F. A. Merchant of the Department of Veterinary Hygiene, Iowa State College, supplied us with Strains P.M. 195 and J.S.B. I. The 14 strains of *P. multocida* recovered from Norway rats by the methods described above were employed in addition.

Hemolysis: The capacity of the strains to hemolyse rabbit blood was tested by incubating them for 48 hours on agar plates containing 10% rabbit blood at 37°C. Only the bovine strain, PM195, caused hemolysis, and by its fermentation of lactose and maltose proved to be a true *Pasteurella hemolytica*. According to most workers, this is an atypical *Pasteurella multocida* and apparently deserves a separate classification.

Bipolarity: Bipolarity was observed in smears of 18 hour broth cultures stained for 2 minutes with Methylene blue. This simple staining method was satisfactory for demonstrating bipolarity and, moreover, can be used easily in any routine diagnostic laboratory. Bipolar staining was especially clear after animal passage, and in our belief, doubtful bipolarity may be accentuated by animal passage.

Motility: Motility was studied in a hanging drop preparation of 18 hour broth cultures. No strain was found to be motile.

Growth on Potato and Desoxycholate media: All strains grew well in plain infusion broth and on rabbit blood agar plates. None of the strains tested showed growth on plain potato or desoxycholate agar plates.

Indol Production: All strains formed indol in peptone-water at 48 hours incubation, but there was a marked difference in indol production among the various strains. Strain Fl. I gave only a slightly positive reaction after 4 days of incubation.

Litmus Milk: Change in color was read after 10 days incubation. Only Strain PM195 gave a definite color change, becoming red after 3 days incubation.

Catalase: The presence of catalase was demonstrated by the release of oxygen from hydrogen peroxide poured over an 18 hour culture on a plain agar slant.

Bile Solubility: Two drops of ox bile were added to 1 cc. of 18 hour infusion broth culture of each strain. No strain was bile soluble.

Pathogenicity for mice and rabbits: Each strain was tested for pathogenicity as described above. Only Ct. I and P.M.195 were found to be non-pathogenic for mice.

Fermentation reactions: The ability of each strain to ferment various carbohydrates was tested by inoculating several drops of an 18 hour broth culture into broth containing 1% of the test-substance and incubating at 37°C. The production of acid and gas was observed, at intervals, for 15 days. None of the strains produced gas but all strains produced acid slowly in 4 to 10 days on certain substrates. Strain P.M.195 produced acid much more rapidly.

Rosenbusch-Merchant Groups. Rosenbusch and Merchant (17), when studying 114 strains of *Pasteurella multocida*, were able to divide these strains into two groups on the basis of fermentation reactions and serological characteristics. They found that arabinose, dulcitol, and xylose fermentations were sufficient to set up classification of these groups. Group I fermented arabinose and dulcitol, but not xylose; it included some strains from all animal species tested. Group II fermented only xylose; it also included some strains from all animal species tested, except birds. Another small group did not give uniform fermentation reactions; it consisted mainly of ovine-bovine strains, and cross agglutinated poorly with the other groups. As will be seen in Table IV, six of our Norway rat strains cannot be classified in any of the Rosenbusch-Merchant groups. Of the other rat strains, 5 belong to Group I and one conforms to Group II. It should be noted that insufficient fermentation tests were carried out on two of the rat strains to permit classification by this method. This was due to their loss as a result of our failure to realize the necessity of frequent (preferably weekly) passage through broth into fresh blood agar. It was found inadvisable to preserve cultures, without passage, in the icebox for longer than 10 days.

Serology

Cross-agglutination of *P. multocida* strains was studied. All strains listed in Table IV were included. The results of this comparative study are shown in Table V.

Preparation of Anti-serum: Specific anti-sera were prepared from three rat strains (WR2b, WR38, WR48) and one fowl strain (Fl. 1).

Rabbits were inoculated intravenously with heat-killed vaccine in increasing dosages over a period of 30 days. Each rabbit received a total dose of 15 cc. and was bled the first and thirtieth day. The serum of the first bleeding was taken as the normal rabbit serum control. The vaccine consisted of a suspension in physiological saline of the bacterial cells obtained from 20 hour infusion broth cultures.

TABLE V

Agglutination tests of Pasteurella multocida strains with specific rabbit antisera

PASTEURELLA STRAIN	HOST ORIGIN	AGGLUTINATION TITRE BY SERUM				NORMAL RABBIT
		WR2b	WR38	WR48	Fl 1	
WR2b	Norway rat	0	0	0	0	0
WR3b	Norway rat	0	1/1280	0	0	Neg.
WR7	Norway rat	1/1280	1/2560	1/320	1/2560	Neg.
WR9	Norway rat	1/1280	1/2560	1/320	1/2560	Neg.
WR11	Norway rat	1/1280	1/1280	1/320	1/2560	1/40
WR25	Norway rat	1/1280	1/1280	1/320	1/1280	Neg.
WR37	Norway rat	1/2560	1/2560	1/320	1/1280	1/40
WR38	Norway rat	1/2560	1/5120	1/320	1/2560	Neg.
WR45	Norway rat	1/1280	1/1280	1/640	1/2560	Neg.
WR47	Norway rat	1/2560	1/640	1/2560	1/320	Neg.
WR48	Norway rat	1/1280	1/640	1/5120	1/1280	Neg.
WR49	Norway rat	1/1280	1/1280	1/640	1/1280	Neg.
WR67	Norway rat	1/1280	1/2560	1/640	1/2560	Neg.
WR81	Norway rat	1/1280	1/2560	1/320	1/2560	Neg.
Rt. 1	Rabbit	1/1280	1/2560	1/2560	1/320	Neg.
Fl. 1	Fowl	1/1280	1/1280	1/320	1/5120	Neg.
Ct. 1	Cat	1/2560	1/2560	1/640	1/640	Neg.
PM195	Cow	Neg.	Neg.	Neg.	Neg.	Neg.
JSB 1	Sheep	1/640	1/640	1/160	1/320	1/40

0 = not done.
Neg. = negative.

The cells were washed three times, concentrated ten times, killed by heating one-half hour at 63°C., and tested for sterility.

Preparation of Antigen: Initially, 20 hour agar plate cultures were used, but later 20 hour rabbit blood agar plates with 1% added sucrose were found to yield richer, more mucoid growth. The bacterial cells washed from the plates with sterile saline were killed with 0.5% formalin. Antigen prepared from the rabbit blood agar plates with

1% sucrose is supposed to be more stable and exhibited less auto-agglutination.

Agglutination Technique: Serial dilutions of the different anti-sera, ranging from 1/40 to 1/10, 240, were prepared in physiological saline and were incubated with each antigen in a water bath of 41°C. as described above under animal pathogenicity. Readings were made after 24 to 48 hours incubation, and again after standing over-night in the icebox. Normal rabbit serum controls were run, and each test was repeated twice. Whenever auto-agglutination occurred, fresh antigen was prepared and the test repeated.

Results: As shown in Table V, homologous agglutination titers ranged from 1/2560 to 1/5120, final dilution of serum. Normal rabbit serum never agglutinated in a dilution above 1/40. The bovine strain did not agglutinate with any anti-sera. It will be seen in Table V that all other strains cross-agglutinated.

The antigenic similarity of all the strains tested, with the exception of the cow strain PM195, is apparent. There seem to be minor differences between certain of the strains, but these antigenic differences do not correlate with the differences noted by the fermentation tests recorded in Table IV. It is of interest that the 6 strains (WR37, WR38, WR45, WR48, WR67, WR81) which could not be placed in one of the Rosenbusch-Merchant groups by fermentation tests, nevertheless are antigenically similar to the other strains tested. This is contrary to the findings of these workers (17) and suggests that these 6 rat strains represent a separate group different from any by them encountered.

Sixty human sera, several obtained during convalescence from patients with fever of unknown origin, were tested for agglutination with *P. multocida* antigens WR38 and Fl. 1. Except for an occasional 1/40 titre, the agglutinations were negative. In addition, convalescent sera from three patients with Brucellosis, 2 patients with Tularemia, and 2 with H. influenzae infection were similarly tested and found to be negative with the *P. multocida* antigen even though these sera showed high agglutinin titers with the homologous antigens. Moreover, *P. multocida* specific rabbit anti-serum was tested for agglutination with *B. melitensis*, *P. tularensis* and *H. influenzae* antigens, with negative results.

Penicillin Sensitivity

One of our *P. multocida* strains (Strain WR38), isolated from the throat-swab of a wild Norway rat, was tested *in vitro* for sensitivity to streptomycin and penicillin. This Pasteurella strain was found to be rather resistant to streptomycin bacteriostasis since 4.5 units/cc. inhibited growth. It did show unexpected sensitivity to penicillin bacteriostasis, growth being inhibited by as little as 0.1 unit per cc.

As extreme sensitivity to penicillin is rather unusual for a Gram-negative micro-organism, penicillin sensitivity tests were done of all the other *P. multocida* strains available and the same unusual sensitivity was found. Certain other Gram-negative rods, which might be confused with *P. multocida*, were similarly tested. All tests were done at least twice.

The method used to test penicillin sensitivity was to inoculate each of a series of tubes of fresh beef infusion broth containing varying amounts of penicillin with an equal volume of the broth containing a 10^{-3} dilution of a 20 hour broth culture of each bacterium. The final concentrations of penicillin ranged from 0.1 unit to 0.9 units per cc. of medium with increments of 0.1 unit per tube. The tubes were incubated at 37°C. and the presence or absence of growth was noted at 24 and 48 hours, subcultures being made in case of doubt. The penicillin employed was the fresh crystalline sodium salt. (Merck)

It will be seen in Table VI that all nineteen of the *P. multocida* strains tested were sensitive to 0.2 units of penicillin per cc. or less. All of the other Gram-negative species tested were resistant to 0.9 units or more. Meyer (19) found that some strains of *P. pestis* were killed by 0.02 units of penicillin, whereas 4 strains of *P. pseudotuberculosis* isolated from different animal hosts were resistant to as much as 1.5 units of penicillin per cc. One starts wondering if it is only a coincidence that of all Gram-negative rods only *P. pestis* and *P. multocida* show this peculiar hypersensitivity to penicillin *in vitro*. Recently a *P. multocida* strain, isolated from wild ducks, was reported to be sensitive to 0.08 units of penicillin per c.c. (42).

DISCUSSION

This study has shown that a certain percentage (14%) of wild Norway rats studied carried virulent *P. multocida* organisms in their

throats. The strains recovered were found to be unusually virulent for a wide variety of animals. The implications of these findings are twofold, (1) concerning the epidemiology of hemorrhagic septicemia in animals and (2) concerning the epidemiology of human cases of pasteurellosis.

TABLE VI

Penicillin Sensitivity of Pasteurella multocida in Vitro

STRAIN	HOST ORIGIN	UNITS OF PENICILLIN PER CC. OF MEDIUM									
		.9	.8	.7	.6	.5	.4	.3	.2	.1	0.
P. multocida WR2b	Rat	−	−	−	−	−	−	−	−	−	+
P. multocida WR3b	Rat	−	−	−	−	−	−	−	−	−	+
P. multocida WR7	Rat	−	−	−	−	−	−	−	−	−	+
P. multocida WR9	Rat	−	−	−	−	−	−	−	−	+	+
P. multocida WR11	Rat	−	−	−	−	−	−	−	−	+	+
P. multocida WR25	Rat	−	−	−	−	−	−	−	−	+	+
P. multocida WR37	Rat	−	−	−	−	−	−	−	−	−	+
P. multocida WR38	Rat	−	−	−	−	−	−	−	−	−	+
P. multocida WR45	Rat	−	−	−	−	−	−	−	−	−	+
P. multocida WR47	Rat	−	−	−	−	−	−	−	−	−	+
P. multocida WR48	Rat	−	−	−	−	−	−	−	−	+	+
P. multocida WR49	Rat	−	−	−	−	−	−	−	−	−	+
P. multocida WR67	Rat	−	−	−	−	−	−	−	−	−	+
P. multocida WR81	Rat	−	−	−	−	−	−	−	−	+	+
P. multocida RtI	Rabbit	−	−	−	−	−	−	−	+	+	+
P. multocida FlI	Fowl	−	−	−	−	−	−	−	−	−	+
P. multocida CtI	Cat	−	−	−	−	−	−	−	−	−	+
P. multocida PM195	Cow	−	−	−	−	−	−	−	−	+	+
P. multocida JSBI	Sheep	−	−	−	−	−	−	−	−	+	+
H. influenzae 1	Human	+	+	+	+	+	+	+	+	+	+
2	Human	+	+	+	+	+	+	+	+	+	+
3	Human	+	+	+	+	+	+	+	+	+	+
4	Human	+	+	+	+	+	+	+	+	+	+
Salm. pullorum	Chicken	+	+	+	+	+	+	+	+	+	+
" suipestifer	Human	+	+	+	+	+	+	+	+	+	+
Paracolon bacillus	Human	+	+	+	+	+	+	+	+	+	+
H. bronchisepticus	Rabbit	+	+	+	+	+	+	+	+	+	+

Growth = +.
No growth = −.

Hemorrhagic septicemia occurs in epidemic form in a wide variety of animals, and its ravages on wild and domestic animal life have long been recognized. Outbreaks of fowl cholera (hemorrhagic septicemia) among chickens have never been explained by the presence of chronic

carriers (20). In flocks studied by the Bureau of Animal Industry of the U. S. Department of Agriculture, it was found (21) that the incidence of fowl cholera was no higher in those flocks having chronic carriers than in those without carriers. Our study has incriminated the rat as a reservoir for virulent *P. multocida*, and considering the close contact of this animal with chickens, the wild rat may well be the missing link in the epidemiology of fowl cholera. Norway rats are known as carnivorous scavengers, and may acquire the carrier state by feeding on animals having died of hemorrhagic septicemia. It can, furthermore, be postulated that the wild Norway rat may play an important role in the epidemiology of hemorrhagic septicemia of other animals. For instance, as yet unexplained is the fact that cats and dogs are sometimes found dead in alleys after having chased rats (22). As was shown in our study, a small inoculum of *P. multocida* may kill these animals by acute septicemia overnight. The possibility of rat bite should always be entertained in the sudden death of domestic animals.

Human cases of pasteurellosis have been ascribed to cat bites, dog bites, etc. (see Appendix), but never to rat bites or contact with rats. How intimate the contact of the wild Norway rat can be with human beings was borne out in a recent study (23) in Baltimore; 95 patients with rat bites were admitted to the Johns Hopkins Hospital alone from an area of less than two square miles during a four year period. We believe that the potentialities of the spread of human pasteurellosis by the rat are great, and that careful search for *P. multocida* should be made in all cases of sickness in human beings following contact with rats.

The extreme sensitivity of the strains of *P. multocida* to penicillin *in vitro* as shown in this study is promising for the control of the disease and may, moreover, prove to be a valuable aid for the identification of this micro-organism. In the belief of many workers (19, 24, 25), *P. multocida* is not infrequently mistaken for H. influenzae in the routine laboratory, and in a summary of the literature of human cases of Pasteurellosis at least 5 were initially misdiagnosed as H. influenzae infections. (See Appendix). Certain strains of *H. influenzae* could easily be confused with *P. multocida* because of similar biochemical characteristics. Moreover, *H. bronchisepticus*, which is known to cause acute respiratory disease in rabbits and dogs and a

whooping cough-like syndrome in children (26), may be confused with *P. multocida* for the same reasons. Our study has shown that both *H. influenzae* and *H. bronchisepticus* are significantly more resistant *in vitro* to penicillin than *P. multocida*. We therefore suggest the use of penicillin sensitivity *in vitro* as an additional laboratory method for the differentiation of *P. multocida* from other Gram-negative rods

Our study has borne out previous observation (27) that the laboratory rat is resistant to infection by *P. multocida*, and has shown that this is also true for the wild Norway rat. It is of interest that other species of rats such as the Cotton rat and Alexander rat are highly susceptible to infection by *P. multocida*. We have failed to demonstrate neutralizing and agglutinating antibodies in the sera of the Norway, hooded or albino rat, but have succeeded in showing rapid phagocytosis in these species. Other factors which may be involved in the natural resistance of these animals have not yet been elucidated.

Our studies of the 14 strains of *P. multocida* isolated from the throats of wild Norway rats have shown that about half could be classified according to the Rosenbusch-Merchant grouping (17); i.e. by biological and serological reactions. Six of our strains defied classification into their groups on the basis of fermentation reactions. Contrary to the findings of the above workers these strains showed antigenic similarity to the strains of the two main groups. Five of these six strains fermented arabinose and xylose but not dulcitol, and thus may represent a separate group. The rest of our strains fell into Group I. It is interesting to note that in the review of twenty human cases of Pasteurellosis (see Appendix), nearly all the strains of *P. multocida* recovered belonged to Group II, which contains strains from all animal species except birds.

On the basis of this study, certain recommendations are made for the routine identification of *P. multocida*. 1. Fermentation reactions are not conclusive for the identification of *P. multocida*. 2. Animal passage will often bring out latent bipolarity. 3. Intraperitoneal inoculation of mice as used in routine laboratories is not a good criterion, as many Gram-negative organisms will kill mice by acute septicemia. 4. Subcutaneous inoculation of *P. multocida* into rabbits will produce a typical pathological picture of hemorrhagic septicemia, valuable for identification of the microorganism. 5. Since almost all

the strains of *P. multocida* studied showed antigenic similarities to each other but differed from the other bacterial species tested, specific antisera may be useful in their identification. 6. Penicillin sensitivity may be used as a rapid *in vitro* test for differentiating *P. multocida* from other Gram-negative rods.

SUMMARY

1. Among 102 wild Norway rats caught in Baltimore, 14 carried virulent *P. multocida* in their throats.

2. These strains of *P. multocida* were unusually virulent for a wide variety of animals, while the Norway rat and laboratory rat were completely resistant. Further studies were made to elucidate the mechanisms of this resistance.

3. Detailed study of the bacteriology and serology of the 14 recovered strains were made, and their classification discussed.

4. All 14 strains and also strains of *P. multocida* from other laboratories were sensitive *in vitro* to less than 0.2 units penicillin/cc. of media.

5. It is suggested that the penicillin sensitivity test *in vitro* be used as an additional method for differentiating *P. multocida* from other Gram-negative rods.

6. A comprehensive summary is included of clinical and bacteriological data concerning human cases of pasteurellosis reported in the world literature from 1930–1947.

7. Evidence is presented that *P. multocida* may be easily confused with other Gram-negative microorganisms, hence it is urged that diligent search for *P. multocida* be made in all cases of obscure infection in animals or human beings.

APPENDIX

Tables VII and VIII present clinical and bacteriological data, respectively, from reports of human pasteurellosis collected from the world literature from 1930–1947. Of more than thirty cases reported since 1930, 21 have been selected as showing the most convincing evidence of true pasteurellosis. An attempt has been made to review in the tables only reports based on good bacteriological studies. Early reports of human Pasteurella infection prior to 1930, have been summarized (28). For this reason, and because 1930 marks the

TABLE VII

Clinical data from reports of human pasteurellosis. (A summary of published cases from 1930–1947.)

REPORT #	AUTHOR	COUNTRY	YEAR	NO. OF CASES	MECHANISM OF INFECTION	TYPE OF DISEASE	PASTEURELLA ISOLATED FROM	DURATION OF ILLNESS	OUTCOME
1	Hundeshagen (29)	Germany	1919	1	Unknown	Pleurisy	Pleural exudate repeatedly	4 months	Complete recovery
2	Kapel et al (5)	Denmark	1930	1	Cat-bite	Infection of hand	Abscess	1 month	Permanent dysfunction of finger
3	Rimbaud (32)	France	1931	1	Unknown	Pleurisy	Pleural exudate	2 months	Complete recovery
4	Slecht (36)	Germany	1931	1	Consumption of infected chicken	Severe hepatitis with icterus	Duodenal washings repeatedly	4½ months	Complete recovery
5	Levy-Bruhl (37)	France	1934	1	Rabbit-muscle used as hemostat	Meningitis	Cerebrospinal fluid	3 days	Death
6	Rivoalen (11)	Morocco	1936	1	Panther-bite	Septiceamia	Blood and abscess	4 months	Complete recovery
7	Foerster (38)	Germany	1938	1	Unknown	Progressive lung disease	Pleural exudate and postmortem	11 years	Death
8	Peltier et al (39)	France	1938	1	Unknown	Acute and fatal septicaemia	Blood and post mortem	10 days	Death
9	Mulder (24)	Holland	1938	1	Unknown	Chronic bronchitis	Sputum	Several years	?

10	Regamey (25)	Switzerland	1938	1	Latent Sinus-infection, to CNS after trauma	Late post-traumatic meningitis	Repeatedly from cerebrospinal fluid	1 month	Complete Recovery
11	Plette (33)	Holland	1938	1	Unknown	Bilateral broncho-pneumonia with pleural & pericardial effusion	Pleural exudate & also post-mortem	Several weeks	Death
12	le Chuiton (34)	France	1939	1	Cranial fracture	Meningitis	Cerebrospinal fluid	1 month	Complete Recovery
13	Weber (6)	Germany	1941	10	Cat-bite	Infection of extremities	Abscesses	1 week–3 months	One amputation of forearm
14	Boisvert et al (12)	U. S. A.	1941	1	Rabbit-bite	Infection of hand & forearm	Abscess	1½ months	Recovery
15	Pestana et al (40)	Brazil	1941	2	Unknown	Pleurisy	Pleural exudate	1 month	Recovery
16	Allin (7)	Canada	1942	2	Cat-bite	Infection of extremities	Abscess	Subclinical 11 months	Recovery
17	Reinders (35)	Holland	1943	1	Latent infection flaring up after trauma (Operation)	Meningitis	Cerebrospinal fluid	1 month	Good recovery

TABLE VII—*concluded*

REPORT #	AUTHOR	COUNTRY	YEAR	NO. OF CASES	MECHANISM OF INFECTION	TYPE OF DISEASE	PASTEURELLA ISOLATED FROM	DURATION OF ILLNESS	OUTCOME
18	Ludlam (41)	Scotland	1944	1	Unknown	Appendicular abscess	Pus of abscess	Several weeks	Recovery
19	Allot et al (8)	England	1944	7	Cat and dog bite	Infection of extremities with sub-acute osteomyelitis	Abscesses	Weeks to several months	Recovery
20	Hansmann et al (9)	U. S. A.	1945	2	Cat bite	Infection of extremities	Abscesses	1 week to months	Recovery
21	Cooper et al (10)	England	1945	1	Cat bite	Infection of hand	Abscess	6 weeks	Recovery
22	Thjotta et al (43)	Norway	1946	1	Unknown	Pneumonia with empyema	Pleural exudate	?	Recovery

beginning of reports of human pasteurellosis caused by animal bites, (5), our summary extends from that date. One additional case, (29) reported in 1919 by Hundeshagen in Germany is included because it is regarded as the first well-reported case in the literature, and because it occurred during the influenza pandemic of 1919. During this pandemic, many Gram-negative Pasteurella-like organisms, showing bipolar staining, were isolated from cases of pneumonia (30, 31). Identification was never conclusively established, although most cases were classified as due to *H. influenzae*. As is known, *H. influenzae* may closely resemble *P. multocida* in its bacteriological characteristics, and it is possible that more cases of Pasteurella infection were overlooked during the pandemic. Also, in our summary, it will be found that the initial diagnosis of *H. influenzae* infection was made in at least five cases (cases 24, 25, 29, 32, 33) subsequently proven to be infections by *P. multocida*.

The varying mechanisms of infection and the wide variety of clinical manifestations will be noted in Table VII. It is of considerable interest that *P. multocida* may apparently lie dormant in tissue for months, giving rise to an acute infection after traumatization of the sub-acutely infected tissue (7, 25, 34, 35).

Table VIII presents the bacteriological data of the strains of *P. multocida* isolated from these human cases of pasteurellosis. It should be mentioned that all strains were Gram-negative, non-hemolytic, non-motile, and showed growth on plain agar, did not ferment lactose, and produced indol. Bipolarity was demonstrated in some instances only after animal passage. Odor and H_2S production are shown to be worthless criteria. The sugars most frequently fermented by the various strains of *P. multocida* were dextrose, glucose, levulose, and saccharose. It is interesting to note that the majority of the strains fall into the Rosenbusch-Merchant Group II, i.e. they ferment xylose, but not arabinose and dulcitol. Group II was shown by them to represent strains from all animal species except birds, and it is intriguing to speculate on the apparent lack of avian strains in this summary.

The help given by Dr. Curt P. Richter and Dr. David Davis has been indispensible for this study. Also gratefully acknowledged are the valuable suggestions of Dr. Karl F. Meyer.

TABLE VIII

Bacteriological data from reports of human pasteurellosis. (A summary of published data from 1930–1947) See Table VII

REPORT	BIPOLARITY FIRST DETECTED			BIOCHEMICAL TESTS																		ANIMAL PATHOGENICITY							AGGLUTINATION OF				SPECIAL REMARKS
	Direct smear	Culture	After animal Passage	Odor	H_2S Production	Growth on Potato	Dextrose	Glucose	Sucrose	Saccharose	Levulose	Maltose	Xylose	Galactose	Mannite	Arabinose	Dulcitol	Sorbitol	Mannose	Mouse	G-pig	Rabbit	Canary	Pigeon	Dog	Monkey	Patient-serum	Homologous Anti-serum	Control sera	Cross-agglutination with other *P. multocida*	
1			+	+	0	−	A			A	A				A					+	+	+	0	0	0	0	1:200	+	−	+	First thought of H. influenzae
2	+	−		0	0	−		A		A	A		A	A	A	−	−	−	A	+	0	0	0	0	0	0	0	0	0	0	
3			+	0	0	−														0	+	+	0	0	0	0	1:1000	0	0	0	First thought of H. influenzae
4	+			0	0	−	A			A	A	−			A		−			+	0	0	0	0	0	0	0	0	0	+	
5	+			0	0	−		A			A	A							A	+	0	+	0	0	0	0	0	+	0	+	
6		+		0	−	0		A		A					A	−				+	0	+	0	+	+	+	0	0	0	+	
7		+		+	0	0	A			A	A		A		A	−				0	0	+	0	0	0	0	1:1600	1:1600	0	+	
8		+		+	0	−		A		A		A			A					0	0	+	0	0	0	0	0	0	0	+	
9			+	0	0	−		A		A	A	A	A			−	−			+	0	+	0	0	0	0	−	+	0	0	First thought of H. influenzae
10	+			−	0	−		A		A		A	−	A		−			A	+	+	+	0	0	0	0	−	0	−	+	First thought of H. influenzae
11			+	0	0	0		A		A		A			A					+	0	+	0	0	0	0	0	0	0	0	First thought of H. influenzae
12	+			0	0	−	0	A	0	A	A	A	−	A	A	−	−	−	0	+	0	−	0	0	0	0	1/50	1:2400	0	1/320	
13	+		+	0	0	0	A		A											+	0	+	0	0	0	0	0	0	0	0	
14		+		0	0	0	A				A	A			A					+	0	+	0	0	0	0	−	0	0	0	

15		+			+	−	A		A		A		A	A			A		A	0	+	+	0	0	0	0	0	1:800	0	1:800	
16		+	+		−	−	A		A			A	A		A	−		A		+	+	+	0	0	0	0	0	0	0	0	
17		+		0	0	0		A		A				A				A	A	+	0	0	0	0	0	0	−	+	0	0	
18				+	−	0	A		A				A						A	0	+	+	0	0	0	0	1:240	+	0	1:50	
19		+		0	+	0		A	A			−	A			−	−	A		+	0	0	+	+	0	0	−	0	−	0	
20		+		0	+	0	A			A	A	−	A	A			−			+	0	+	0	0	0	0	−	+	−	1:620	
21		+		0	−	−	0	A	A			−	−	A			−	−		+	0	0	0	0	0	0	−	1:1280	0	1:900	
22		+		0	−	0	0	+	+						+					+	+	0	0	0	0	0	1:3200	0	−	0	Resembling diplococci

+ = reaction positive
− = reaction negative
0 = reaction not mentioned
A = acid without gas

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BOOK REVIEWS

Actions of Radiations on Living Cells. By D. E. LEA. Illus. 402 pp. $4.50. Macmillan Company, New York, New York, 1947.

In this monograph, the author has given an excellent quantitative account of certain fundamental actions of x-rays and other ionizing radiations on living cells. The book begins with two chapters briefly discussing the physical properties and chemical effects of ionizing radiations, and then proceeds to discuss in considerable detail the target theory of radiation reaction and its application to problems in genetics and virus inactivation.

Within the chapters devoted to the genetic effects of radiation, a wealth of material has been presented on the structural changes produced by ionizing radiation in the chromosomes of Drosophila melanogaster, Tradescantia, and other animal and plant forms. The frequency with which these changes occur has been considered in relation to the methods by which the several types of radiation have been applied. That many of the changes are caused by single ionizations has been convincingly presented.

The book seems of particular value because it brings together a mass of uncorrelated observations which have been made within the field of radiobiology over a period of years. The data have been given critical quantitative and statistical analysis by which the author seems to provide, beyond all reasonable doubt, a satisfactory explanation of the mechanism by which a small but important number of radiation reactions occur. The book should therefore constitute an excellent guide to those workers who may wish to apply ionizing radiations as tools in the investigation of many fundamental biological processes.

The book is well printed and it is of convenient size for ready reading. The graphical illustrations are clear and demonstrate satisfactorily the data which the author wishes to show. Certainly the book is a valuable contribution to the field of radiobiology.

R. H. M.

Allergy in Theory and Practice. By ROBERT A. COOKE. Illus. 572 pp. $8.00. W. B. Saunders Company, Philadelphia, Pennsylvania, 1947.

This volume is a comprehensive presentation of the many scientific and clinical problems which the physician encounters in the field of allergy. In the foreword, the author states that "instruction in allergy has lagged in spite of its steadily increasing importance, as evidenced by its basic significance and broad applicability in the theory and practice of medicine and its various sub-divisions." The reviewer heartily endorses this statement. It is gratifying indeed to have in our libraries a book that so thoroughly and accurately covers this special field.

The work is a compilation of formal lectures which the author and the "New York Group," sponsored by the American College of Physicians, have presented so ably during the past few years to post-graduate students of allergy. With few

exceptions, the contributors have been students of the author and have worked under his direction for many years; naturally, his conservative judgment is reflected in the writings of these associates.

The lectures are divided into nine sections and an appendix. Within these nine sections, all fundamental aspects of allergy are discussed at length. Although there are differences of opinion concerning the mechanism of the "skin sensitizing antibody" and the "inhibiting antibody," the author gives an appraisal that is fair to each group of investigators.

Section I, devoted to the pathologic-anatomic aspects of allergy, emphasizes the role of allergy in disease. Although this section is brief, the discussion on the immuno-chemistry of allergens and antibodies is inclusive and instructive.

Sections II and III concern allergy of the respiratory tract. To an exceptional degree, this clinical discussion is concise and helpful. Unfortunately, the arrangement is not chronologic, for example, non-infective and infective asthma are discussed before hayfever and rhinitis are presented; yet the latter two conditions, in clinical practice no less important than the former, are often the fore-runners of the more serious complaints. The part relating to the differential diagnosis of bronchial asthma is condensed to five pages; thus, the information presented is little more than an outline. More importance should have been ascribed to this portion of the book, whether the publication is for the post-graduate student or for the under-graduate student.

Section IV, "Allergy of the Skin," is a compilation of lectures by the author, by Louis Schwartz, and by Dudley D. Stetson. Allergic dermatitis is so important in chemical industries, even in less hazardous occupations, that too much emphasis cannot be placed on this manifestation. These lectures adequately discuss the mechanism of allergic dermatitis, the occurrence of various types of dermatitis, and the treatment of the different clinical problems that are encountered.

Less understood allergic problems are discussed in Section V (Allergy of the Nervous System) and in Section VI (Allergy of the Cardiovascular System). The lectures in Section VII relate to other specialties: Allergy of the Digestive System; Allergy of the Eye; Allergy of Infancy and Childhood. The discussion of gastro-intestinal allergy is conservative, and is in complete agreement with the experience of the reviewer. However, there are other physicians, also interested chiefly in allergy, who will consider this section too conservative, even inadequate.

In Section VIII there are a number of subjects which have been given special consideration by the author: for example, Bacterial Allergy in Relation to Diseases of Allergy; Inhalants; Foods and Drugs in Relation to Diseases of Allergy; and finally Physical Allergy. Many of the unusual reactions of these allergens are clearly explained in this series of lectures. Section IX should be especially helpful to the laboratory assistant. The discussion of skin testing, of preparation and standardization of extracts, and of laboratory procedures should prove particularly helpful to those physicians who contemplate the special field of allergy.

Page 148 contains a statement to which the reviewer must take exception. The author states that he does not concur in the belief that opium and its derivatives

should never be used in asthma. That many asthmatic patients have died following the injection of a small dose of morphine must be well known to the author and to other physicians with training in allergy. Death was due to sudden paralysis of a fatigued respiratory center in a patient who had been struggling for oxygen over a period of hours. Because such reactions cannot be foretold, I emphasize that the use of morphine in asthma is too dangerous a procedure.

In the appendix the author mentions, as if it were an afterthought, "a revival of interest in psychic and nervous factors in relation to disease—so-called psychosomatic medicine." Only two short paragraphs are devoted to this important subject, and the reviewer is given the impression that the author is not impressed with the importance of nervous factors in relation to allergic diseases. Of course, psychic factors cannot produce an allergic state, but pseudo-allergic states would not be diagnosed as "allergic" if specialists in the field of allergy were better psychiatrists. This is true especially in the study of patients suspected of an allergy to foods.

In general this is an excellent presentation, discussing and clarifying the theory, the clinical manifestations, and the treatment of allergic diseases. This volume will be most enlightening to all internists and to students who contemplate the practice of internal medicine.

L. G.

Bacteriology, Laboratory Directions for Pharmacy Students. 2nd Ed. By MILAN NOVAK and ESTHER MEYER. 247 pp. C. V. Mosby Company, St. Louis, 1947.

This manual of laboratory exercises for thirty-six periods is quite comprehensive and should provide an excellent course for either pharmacy or medical students. Methods, viewpoints and objectives are so diverse in bacteriology that every teacher in this field will find it easy to criticize a course outlined by others without implying criticism of the authors. Another factor which makes it difficult to publish a manual, which may be used to advantage in a number of schools, is the time factor. Not only the length of the course, number of exercises, but also the distribution of hours and days scheduled during the course may necessitate complete rearrangement of the material. Bacteria are living, growing organisms that do not skip idle days nor rest on Sunday. For this reason most teachers of bacteriology do and should write their own outlines. In doing so they frequently find valuable suggestions and material in such manuals as the one here reviewed.

J. H. B.

Brown-Sequard, Charles-Edouard; A Nineteenth Century Neurologist and Endocrinologist. By J. M. D. OLMSTEAD. 253 pp. $3.00. The Johns Hopkins Press, Baltimore, Maryland, 1946.

This book comprises a recent course of lectures given at the Johns Hopkins Institute of the History of Medicine. It is a well-documented account of the life and achievements of one of the great nineteenth century physiologists. The author,

Dr. Olmstead, the Professor of Physiology at the University of California, is excellently fitted to evaluate the work of his fellow-physiologist. His appraisal of Brown-Sequard's scientific contributions forms the most valuable feature of the book. He shows well the extraordinary mixture of careful investigation and uncritical nonsense that characterized this "eccentric genius." The impetuous intuitive French approach to scientific investigation, and the frequent tendency to build sweeping generalizations on single observations are seen here, yet often the results are brilliant and the contributions lasting. There is some interesting discussion of the relative merits of pure and applied science, and also of the inter-relationship between medical research, teaching, and practice. Little attempt is made to portray the character of the man or the environmental forces that influenced his development. The biographical portion of the book is essentially factual, with the author's interpretive efforts being applied to the work of the scientist rather than to his personality. The book is attractively printed and well bound. It should be of interest to everyone interested in the development of neurophysiological thought during the last century.

G. G. M.

Handbook of Commonly Used Drugs, A. By MICHEL PIJOAN and CLARK H. YAEGER. 198 pp. $3.75. Charles C. Thomas, Springfield, Illinois, 1947.

The authors have attempted to present, in highly abbreviated form, a résumé of current drug usage. The preface states that their purpose "is not to replace standard text-books of pharmacology, but to act as an adjunct and a guide in conditions where such texts are relatively unavailable." The presentation is somewhat on the model of Goodman and Gilman's "The Pharmacological Basis of Therapeutics." Thus each discussion of a drug is preceded by a short section on its structure and physiological effects. The discussion of the drugs as therapeutic agents is so brief as to cause confusion. This is particularly true in the chapter on sulfonamides. The toxicity of drugs is inadequately covered.

Chapter XVII contains some 45 pages (25 per cent of the text) on the treatment of tropical diseases. Many of these diseases have no specific treatment, so that the discussion of the disease is perforce limited to etiology, epidemiology and prevention. In the section on malaria, it should be pointed out that the suppressive regimen recommended for quinacrine (0.05 gm. daily and 0.1 gm. on Sundays) is lower than that found to be necessary by the Army. The suppressive regimen recommended for SN 7618 (0.3 gm. daily) is 5–6 times in excess, and approaches the toxic range.

The book is marred by an excessive number of errors of typography and spelling, so that it cannot be depended upon as a factual guide. One particularly serious mistake is that the metric hypodermic dosage of morphine is stated to be 0.515 grams. The structural formulas for neocinchophen, quinacrine, dilantin, homatropine, scopolamine, and other substances, are incorrect.

Because of dangerous brevity and the large number of errors, this book fails to fulfill its avowed purpose.

C. G. Z.

If You Need an Operation. Dr. RICHARD A. LEONARDO. 198 pp. $3.00. Froben Press, New York, New York, 1947.

There is a great demand for popular books on medical subjects. Dr. Leonardo, whose facile pen has produced several rather successful books on medical history and philosophy, here turns his attention directly to the needs and worries of the laity. This book is a particularly useful one in its field and could be safely given to most intelligent patients. It answers their questions adequately and plainly and at the same time would not seem to implant new worries in their minds.

H. N. H.

Jewish Luminaries in Medical History. By HARRY FRIEDENWALD. 199 pp. $3.00. Johns Hopkins Press, Baltimore, Maryland, 1946.

A scholarly little work for scholars. This lecture by Doctor Friedenwald, with a foreword by Henry Sigerist, is not merely pleasantly informative but is a key to the other monumental work, "The Jews In Medicine." It is a sine qua non for anyone interested in the history of medicine. The lecture and the list of titles serve alike to note some of the great Jewish figures in medicine and to emphasize the value of the continuity of their cultural thread.

C. R. A.

Penicillin in Syphilis. By JOSEPH EARLE MOORE. Illus. 319 pages. $5.00. Charles C. Thomas, Springfield, Illinois, 1946.

In several ways this is a fascinating book. It discusses all of the general points relating to penicillin as far as were known at the date of publication, October 1946. It presents an accumulation of information, of clinical data, and of experimental work that has not been brought together elsewhere. And it is an outstanding example of the product of cooperative investigation.

This book records the work of 52 groups of clinics including four installations of the U. S. Army, one of the Navy, thirteen of the U. S. Public Health Service Rapid Treatment Centers, twenty-six civilian clinics, and eight laboratories of experimental syphilis. Never before has such widespread and intensive investigation been directed at any one therapeutic problem. The results are brilliant and satisfying. It should be pointed out that this cooperative method is possible only when established and uniformly organized clinics are available and when general interest and financial support center on one aspect of a clinical subject. This variety of cooperation was developed as a military measure during the last war. The technique of such studies should continue to be useful in certain instances during peacetime. One must not forget, however, that without the impetus of war, each clinic and laboratory will revert to its own research pattern in preference to a pattern submitted by a central agency.

Dr. Moore has an easy, refreshing, and sometimes dramatic style. The mass of material covered in this book is presented smoothly and interestingly. Even when the reader finds himself in slight disagreement with the conclusions that are put forth, he recognizes the thought behind the written word and appreciates that much that is discussed in this book is still in the process of being discovered.

There are something over 249 references to current literature. The index is excellent. This is a book that no one who is interested either in penicillin treatment of infectious diseases or in the treatment of syphilis can miss with impunity.

H. M. T.

Rehabilitation Through Better Nutrition. By TOM D. SPIES. Illus. 94 pp. $4.00. W. B. Saunders Company, Philadelphia, Pennsylvania, 1947.

"The purpose of this monograph", Dr. Spies writes, "Is to call attention to the fact that we have shown that persons debilitated solely by nutritional deficiencies gain strength promptly following specific nutritive therapy." With this in view, Dr. Spies has summarized the experiences of the Nutritional Clinic at the Hillman Hospital, Birmingham, Alabama. Here, as elsewhere, nutritional deficiencies were observed not only in the indigent, but in those with erroneous dietary habits, food idiosyncracies or organic disease which interferes with the ingestion or utilization of food, in pregnant and lactating women and persons whose physical exertions have increased, and in persons chronically addicted to alcohol as well. Spies speaks of malnutrition as "primary" when it is the result of failure to eat an adequate diet, and "secondary" when the result of disease. He emphasizes that in human beings it is rare to see a naturally occurring deficiency of a single nutrient, a concept which we assume he limits to the adult age group. Instead he prefers to speak of "nutritive failure", a term describing a variable clinical picture as the result of the failure of one or more specific nutrients. Indeed, Dr. Spies believes that no two patients present the same clinical manifestations of deficiency. The rôle of adequate nutritional therapy in the rehabilitation of the malnourished was tested on 914 patients, selected because they were non-alcoholic adults, potentially capable of work, without serious organic disease, who had diagnostic evidence of one or more deficiency diseases and nutritive failure severe enough to prevent their working. These patients were treated in accordance with four therapeutic principles. Conditions causing excessive needs for the essential nutrients were relieved; co-existing disease was treated symptomatically; a liberal and well balanced diet was supplied, and the diet was supplemented with synthetic nutrients or concentrates. Treatment was not regarded as satisfactory until the patient had regained strength, his weight had returned to normal, and he was able to return to work and to continue to work regularly. Impressively, on this regime 893 patients were restored to gainful employment.

This manual was designed as a guide to therapeutics in nutritional failure for the use of medical students and physicians. With this in view, clinical descriptions of various deficiency states, illustrative case histories, and specific dietary and therapeutic regimens have been included. It is unfortunate that the brevity of the monograph has precluded greater detail in the description of the clinical pictures encountered, as well as the pathologic and experimental basis for the assignment of specific symptoms to specific deficiency states. Similarly the lack of a comprehensive bibliography limits the utility of this book to students of

nutritional disorders. These omissions lend the book a didactic air which does not jibe with Dr. Spies' own caution in the diagnosis of deficiency states. The monograph, however, is a useful exposition of the value of careful clinical analysis and aggressive therapy in the management of patients with nutritive failure.

O. D. R.

Sex Education: A Guide for Parents, Teachers and Youth Leaders. By CYRIL BIBBY. 311 pp. $3.50. Emerson Books, Inc., New York, New York, 1946.

This book, written in recognition of the increasing need for a simple but comprehensive discussion of the subject matter of sex education, should prove to be a very helpful, practical guide for all those who are becoming more and more aware of the importance to provide our youth with well planned information on the topic.

The author devotes a large portion of the discussion to the integration of sex education with other subjects in school, while relegating the major responsibility for its teaching to persons outside the home. He does so with the intention of deemphasizing the special position sex has been given in the past and thus make it merely one aspect of one's biological development. The majority of parents, more unable than unwilling to assume the rôle of teaching, will welcome the school teacher's readiness to perform the difficult task for them, according to the author; discussions on the topic per se by itinerant lecturers should be limited to the exceptional occasion.

The book includes simply presented factual information on most all sexual topics while at the same time providing the instructor with the type of vocabulary most useful to convey the information to children; this is done by illustrative answers to questions which are likely to be submitted by them. With some justification, the author minimizes the position of the family physician in sex education, stressing his lack of educational ability and experience. On the other hand, it might be said about school teachers that they are by no means qualified to teach sex by virtue of their other educational experience. The author recognizes this point by advocating improvement in the curriculum of teachers' colleges.

All in all, the book is a courageous and successful attempt at clarification of an issue which, unfortunately, is still controversial. It should be read by everyone who has close contact with children and adolescents.

E. A.

Surgeon's Domain, A. By BERTRAM M. BERNHEIM. 253 pp. $3.00. W. W. Norton and Company, Incorporated, New York, New York, 1947.

This book is an attempt to describe the life of a surgeon in everyday language for the lay reader. The success of Dr. Bernheim's other recent publications testifies to the popularity of such writing. The book contains many personal reminiscences of the early days at Hopkins.

H. N. H.

Surgical Treatment of the Soft Tissues. By F. W. BANCROFT AND G. H. HUMPHREYS. Illus. 520 pp. $15.00. J. B. Lippincott Company, Philadelphia, Pennsylvania, 1946.

This is a useful volume with chapters contributed by competent authors on a somewhat heterogeneous group of subjects. There is a sensible discussion of treatment of hernia and cryptorchidism. The results of treatment in the fields of plastic and maxillo-facial surgery are shown by pictures. There is a review of the physiologic alterations following burns, accompanied by description of a wide variety of local treatments, many of them now abandoned, and a voluminous bibliography. General and special infections of the soft tissues are taken up. There is a good discussion of chemotherapy, already somewhat out of date. Benign and malignant neoplasms of the breast and other soft tissues are satisfactorily covered. There is a valuable summary of the uses and limitations of x-ray therapy of neoplasms. An excellent essay on surgery of the large arteries by Herrmann and Reid is the highlight of the book. Here general principles and particular regions and problems are admirably clarified. The surgery of the veins and lymphatics is discussed helpfully.

It would be well in such compilations if the authors would be content with and agreed upon a definite limited audience. The reader who operates on aneurysms need hardly be told how to treat a lymphangitis or incise a paronychia. Parts of this book are too technical for the uninitiated, and others too elementary for the practicing surgeon.

W. E. G.

Synopsis of Operative Surgery. By H. E. MOBLEY. 2nd ed. Illus. 416 pp. $6.00. The C. V. Mosby Company, St. Louis, Missouri, 1947.

This book presents all the standard operative procedures in a brief form, accompanied by suitable illustrations that give a clear understanding of the principle of the operation, but not elaborating on any of its details. It also tabulates the indications for the various procedures, but without discussion of the diagnosis or prognosis. It is not intended either as a textbook or system of operative surgery for the surgical specialist, but as a quick reference for those not too familiar with the various types of operation and interested more in the general scope of the operation than in its technical details. For this latter purpose it is excellent and should be useful to the returning veteran, the medical student, and those preparing for examination in surgical subjects.

R. T. S.

Tuberculosis As It Comes And Goes. By EDWARD W. HAYES, with Chapters by LAURENCE DE RYCKE. 2 Ed. 220 pp. $3.75. Charles C. Thomas, Springfield, Illinois, 1947.

The second edition of "Tuberculosis As It Comes and Goes" brings to date valuable information for the instruction and understanding cooperation of the tuberculous patient with his doctor. Clearly and with accuracy the essential

facts are set down, and the only criticism of the text is that it assumes a familiarity with many terms that the average layman lacks. Perhaps this has a purpose—to have him seek such as a form of occupation and for emphasis! The chapters by Laurence de Rycke are done expecially well and are to be commended to all who have any type of chronic incapacitation.

The book is entitled to a high place among those published for the guidance of all taking the "cure" for tuberculosis.

C. R. A.

Uterotubal Insufflation. By I. C. RUBIN. Illus. 453 pp. $10.00. C. V. Mosby Company, St. Louis, Missouri, 1947.

In this well illustrated monograph of 453 pages Rubin has presented the subject of uterotubal insufflation and allied subjects as no one else could have done. No other gynecologist has had the extensive experience of the author, and no one has at his disposal such a great volume of carefully kept records. The monograph summarizes Rubin's experiences in his great contribution to gynecology. The material presented, however, is not limited to Rubin's but is also drawn from the literature. Nevertheless, it is a personal book, and, when one has read it, he cannot fail to know Rubin's views on the various phases of the subject.

Although a clinical point of view is maintained throughout, the first four chapters are concerned with the anatomy, pathology, and physiology of the fallopian tube.

The second part of the book covers the technique of tubal insufflation and diagnosis. It takes up in detail indications and contraindications for insufflation. The most favorable time for uterotubal insufflation is discussed, and the physical signs and symptoms associated with gas in the peritoneal cavity are described. The varied causes of tubal occlusion are also considered.

The third part of the book considers the therapeutic aspects of tubal insufflation for relief of sterility. Here, Rubin calls attention to the partially or lightly occluded tubes which he believes may be opened often by insufflation. He reports his own series of 3,200 cases, 590 of which subsequently became pregnant. It is noteworthy that 228 or 38.64 per cent of the 590 women became pregnant within two months after insufflation. Rubin also presents statistics from 65 other gynecologists, showing pregnancies occurring in 1.1 per cent to 39.0 per cent of the women upon whom the test was done.

In Chapter 11 Rubin discusses operations for restoration of tubal patency, particularly in their relation to tubal patency tests. He concludes that laparotomy for plastic tubal reconstruction is justified "where the patient is particularly anxious to become gravid and is willing to leave no stone unturned in the effort." He quotes results from a variety of authors. Probably the best cross section of results in this country is shown by Greenhill's report of questionnaires from most of the representative gynecologists. Only 4.4 per cent of the operations resulted in living babies. For comparison, Rubin calls attention to the therapeutic results of tubal insufflation in those cases in which tubal patency was improved after a

second and third insufflation. He had 438 patients falling into this category and 15.07 per cent of them became pregnant. It thus becomes apparent that surgery is never indicated until the therapeutic possibilities of repeated tubal insufflation have been exhausted.

The fourth part is concerned with a comparison of insufflation and lipiodol injection. Much space is devoted to relating the shortcomings and dangers of lipiodol injection. It appears to the reviewer that the author substantiates his objections to lipiodol injection with sound pathological and clinical data. The author also discusses the possibility of harm from insufflation with CO_2. He justly concludes that "the untoward results from lipiodol injection outweigh in number and severity the accidents from CO_2 uterotubal insufflation, and that the latter are more avoidable, a circumstance which appears to be inherent in the nature of the medium."

A chapter is devoted to insufflation in relation to relief of dysmenorrhea. Although he quotes favorable results by Moench and Peterson, Rubin wisely states that "Final conclusions as to the therapeutic effect of tubal insufflation on dysmenorrhea cannot be drawn because they are as yet based upon too small a number of cases."

Finally, the results of most of the gynecologists of the country with tubal insufflation, as obtained by questionnaire, are recorded. If the answers to the questionnaire show nothing else, they at least demonstrate that tubal insufflation has become an accepted and much used procedure by practically all of the gynecological and obstetrical world.

The book can be used with profit by all gynecologists, obstetricians, and many general surgeons whose work includes the investigation and treatment of infertility.

R. W. T.